Society for Endocrinology

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THE ENDOCRINOLOGIST

THE MAGAZINE OF THE SOCIETY FOR ENDOCRINOLOGY

Endocrinology of the gut
unravelling the complexities

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A word from THE EDITOR...

Welcome to 2016. Not to be outdone by current UK political trends, *The Endocrinologist* team has had a bit of a cabinet reshuffle since the last issue. I know the new editorial team are all revved up to continue to make this a magazine worth reading, and relevant to both clinician and scientist alike. My sincere thanks go to Miles Levy for being such a brilliant editor, a supportive colleague ... and a tough act to follow! He's far too good to let go completely, so watch out for a guest appearance in the future.

We kick off this year with a focus on the gut, an organ system far more complex than a simple conveyor belt for your dinner, and one which endocrinologists have rightly reclaimed.

On the menu, especially prepared for the uninitiated, Paul Richards serves up a primer on the basic building blocks of the enteroendocrine system. Tricia Tan and Stephen Bloom then provide a timely update on the burgeoning therapeutic potential of gut hormones. In case you have yet to dive into the world of the microbiome, Roman Stilling and colleagues raise the provocative thought that you might just be acting in service of the controlling army of gut microbes that are making their presence felt in almost all branches of human pathophysiology. And, for those of you who have, to date, been baffled and bemused by the coloured blobs on functional MRI scans acquired from people thinking about/looking at/eating food, Paul Fletcher has written a refreshingly honest piece that debunks myths and provides a framework for clear thinking about what these studies can – and cannot – tell you.

Finally, many thanks are due to all who continue to contribute and give so generously of their time and talent. Please do get in contact with ideas and thoughts. We cannot do it without you.

Wishing you all only good things for 2016.

BEST WISHES

TONY COLL

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70 years on

Become a contributor... Contact the Editorial office at **endocrinologist@endocrinology.org**

The Society welcomes news items, contributions, article suggestions and letters to the Editor. We would also like to hear your feedback on this issue of the magazine.

Deadline for news items for the Summer 2016 issue: **21 March 2016**.
Deadline for news items for the Autumn 2016 issue: **11 July 2016**.

Front cover image ©SHUTTERSTOCK

UPDATES AT *THE ENDOCRINOLOGIST*

Amir Sam

Kim Jonas

We're delighted to welcome Amir Sam (London) as Associate Editor of *The Endocrinologist* and Kim Jonas (London) to the Editorial Board. Our grateful thanks go to retiring Editor, Miles Levy, and retiring Board members Paul Foster and Paul Grant, for all their hard work and input over the last 3 years.

The Editorial Board aims to ensure the views and interests of all Society members are represented in *The Endocrinologist*. If you would like to contact them with your ideas for articles or feedback, please email **endocrinologist@endocrinology.org**.

RECIPIENTS OF NEW GRANTS

The Society's Themed Scientific Meeting Grant aims to support the best new science by funding short, focused scientific meetings. The first of these grants has been awarded to Jason Carroll (Cambridge) – see details in 'Grants' box on this page. The next grant application deadline is 31 May 2016.

Two applications to our Regional Clinical Cases Meetings Grants scheme, which enable the organisation of valuable and informative case meetings across the UK, have been successful. A meeting organised by Fainia Kavvoura and Bahram Jafar-Mohammadi will be held in Oxford, while a second meeting will take place in Norwich, organised by Francesca Swords (details in 'Society supported events' box on this page). The next application deadline for this grant is 15 April 2016.

CLINICAL EXCELLENCE AWARDS 2016

The Society will be supporting members wishing to apply for awards this year. Further details will follow.

WITH REGRET

We were saddened to hear of the untimely death of Jens Sandahl Christiansen of the University of Aarhus, Denmark. Jens was Editor-in-Chief of the Society's journal *Endocrine Connections* and a leading light in European endocrinology. The Society extends its condolences to Jens' family and friends. An obituary will appear in a future issue.

COULD YOU BE A NEW COUNCIL OR COMMITTEE MEMBER?

Ann Logan will retire from the Society's Council in November 2016, having served her 4-year term of office. We would welcome your nominations for her replacement.

In addition, vacancies on the Early Career Steering Group, Nurse, Programme, Public Engagement and Science Committees and Corporate Liaison Board will arise at the end of 2016. Opportunities for two specialty registrars will also arise on the Clinical Committee in the middle of the year, one of which should be filled by an academic trainee.

If you would like to be involved in running your Society, please consider standing for election! Self nominations are accepted. Details and nomination forms are on the relevant Committee pages at **www.endocrinology.org/about/committee.html**. The closing date is 30 June 2016.

CALL FOR MEDAL NOMINATIONS

Medal nominations are sought from members for medallists in 2017. The deadline for nominations is 15 June 2016. A nomination form and more details are available on the Society's website.

MORE ISSUES OF SOCIETY JOURNALS!

You can soon expect high quality publications on a more regular basis. Two Society journals will publish more issues this year. *Endocrine-Related Cancer* will now appear monthly, and the frequency of *Journal of Molecular Endocrinology* will increase to eight issues per year.

SUMMER STUDENTSHIP GRANTS: TAKE YOUR EXPERIENCE FURTHER

The Society's Summer Studentship Grants enable undergraduate students to gain experience in a research environment. They provide £185 per week for up to 10 weeks, plus up to £1,000 for consumables. The grant application deadline is 11 March 2016.

SOCIETY CALENDAR

21–22 March 2016
ENDOCRINE NURSE UPDATE
Birmingham

21–23 March 2016
CLINICAL UPDATE 2016
Birmingham

7–9 November 2016
SfE BES CONFERENCE 2016
Brighton

see **www.endocrinology.org/meetings** for full details

SOCIETY SUPPORTED EVENTS

14 March 2016
REGIONAL CLINICAL CASES MEETING
Oxford

26 April 2016
REGIONAL CLINICAL CASES MEETING
Norwich

15–16 September 2016
HORMONE DEPENDENT CANCERS: NEW THERAPIES AND MECHANISMS OF RESISTANCE
Cambridge

GRANT AND PRIZE DEADLINES

11 MARCH 2016
SUMMER STUDENTSHIPS

15 MARCH 2016
TRAVEL GRANTS

31 MARCH 2016
PUBLIC ENGAGEMENT GRANTS

8 April 2016
EARLY CAREER PRIZE LECTURE ABSTRACTS

15 APRIL 2016
REGIONAL CLINICAL CASES MEETING GRANTS

27 MAY 2016
EARLY CAREER GRANTS

27 MAY 2016
EQUIPMENT GRANTS

31 MAY 2016
THEMED SCIENTIFIC MEETING GRANT

see **www.endocrinology.org/grants** for full details of all Society grants

HOT TOPICS

SOCIETY FOR ENDOCRINOLOGY OFFICIAL JOURNALS

Society members have free access to the current content of *Journal of Endocrinology, Journal of Molecular Endocrinology, Endocrine-Related Cancer* and *Clinical Endocrinology* via the members' area on the Society home page, **www.endocrinology.org**. *Endocrine Connections* and *Endocrinology, Diabetes & Metabolism Case Reports*, the Society-endorsed case reports publication, are open access (OA) and free to all.

JOURNAL OF ENDOCRINOLOGY

Zebrafish as models of mammalian glucagon action

Glucagon is produced by the α-cells in the pancreas and, acting via its receptor (GCGR), it regulates hepatic glucose production. Glucagon antagonism results in hypoglycaemia and can protect against the development of diabetes mellitus, and so it is seen as a potential treatment. However, it is associated with α-cell hyperplasia and tumour growth, the molecular mechanisms for which are unidentified. If you work on human disease, you are probably wary of animal models and may have never gone near a zebrafish, but read on…

Li *et al.* identified two functional (accumulation of cAMP following stimulation) GCGRs in zebrafish. Knockout of these GCGRs in zebrafish larvae results in lower glucose and higher glucagon levels and α-cell hyperplasia. This demonstrates that the compensatory mechanism to glucagon deficiency or interruption of glucagon signalling is conserved in zebrafish, and that GCGR-deficient zebrafish offer an opportunity to unravel the signals that regulate α-cell mass.

Read the full article in *Journal of Endocrinology* **227** 93–103

JOURNAL OF MOLECULAR ENDOCRINOLOGY

IL37 and autoimmune thyroid disease

Hashimoto's thyroiditis (HT) and Graves' disease (GD) differ in clinical presentation and pathophysiology, but both carry thyroid T cells that escape the immune tolerance process and infiltrate the thyroid. Inflammatory cytokines are key in this process.

Yan *et al.* assessed the association of four SNPs (single nucleotide polymorphisms) of IL37 (a natural suppressor of innate and acquired immunity) with HT and GD in the Chinese Han population. The minor A allele of rs2723176/rs2723186/rs3811047 and the minor G allele of rs3811046 were found to have a protective influence on GD susceptibility, but there were no significant associations with HT. Haplotype analysis of IL37 showed that GCG conferred a significant risk for GD, whereas haplotype ACG was associated with an increased risk of HT. Haplotype AAA was significantly lower in GD, indicating a protective role.

The apparent association of the IL37 gene with susceptibility to autoimmune thyroid disease leads us to ask whether there is an IL37 gene risk associated with other autoimmune diseases or autoimmune disease susceptibility.

Read the full article in *Journal of Molecular Endocrinology* **55** 209–218

ENDOCRINE-RELATED CANCER

Clinical implications of androgen receptor in prostate cancer stem cells

Prostate cancer comprises heterogeneous cells that are phenotypically and functionally distinct, which poses clinical challenges as the cell types are likely to respond differently to therapies.

In this review, Deng & Tang discuss prostate cancer stem cells (PCSCs) and heterogeneity of androgen receptor (AR) expression in primary, metastatic and treatment-failed prostate cancers. They hypothesise that, whereas PCSCs in primary and untreated tumours and models are mainly AR^-, those in castration-resistant prostate cancers could be either AR^+ or $AR^{-/lo}$. They discuss the potential mechanisms that the cells may employ to propagate prostate cancer at the population level, mediate therapy resistance, and metastasise.

The authors conclude that targeting AR alone may not achieve long-lasting therapeutic efficacy. Understanding the roles of the AR and PCSCs should provide fresh clues for designing novel therapeutics targeting both AR^+ and AR^- prostate cancer cells.

Read the full article in *Endocrine-Related Cancer* **22** T209–T220

ENDOCRINE HIGHLIGHTS

A summary of papers from around the endocrine community that have got you talking.

Parasites and pregnancies: an unlikely combination?

Pregnancy both alters, and can be affected by, a woman's immunological state. Reasoning that parasitic worm infections can also change systemic immunity, Blackwell *et al.* looked at the link between helminth infection and fecundity.

They studied a community in the Amazonian lowlands of Bolivia, where pharmacological contraceptive use is low (average total births per woman=9) and 70% of the population have a helminth infection. Using 9 years of longitudinal data from 986 women, they found that roundworm infection was associated with earlier first birth and shortened inter-birth intervals. In contrast, infection with hookworm was associated with delayed first pregnancy and an extended inter-birth interval. The effect size appeared surprising large; over a lifetime, hookworm-infected women could expect to have three fewer children than uninfected women, while those with roundworm would have two more.

The potential mechanisms have yet to be fully elucidated, but the immunological response to roundworm may be more favourable to conception and implantation, while the adverse effects of hookworm infection, such as anaemia and nutritional deficiency, decrease reproductive ability.

Read the full article in *Science* **350** 970–972

Hot Topics is written by Rosemary Bland, Dominic Cavlan, Tony Coll, Jennie Evans, Kim Jonas and Amir Sam.

CLINICAL ENDOCRINOLOGY

SHBG levels more strongly associated with obesity than ageing

Total testosterone concentrations are affected by sex hormone-binding globulin (SHBG) concentrations, which in turn are decreased by obesity and increased with ageing. Cooper *et al.* sought to compare the relative associations of obesity and ageing with SHBG.

The authors performed a retrospective analysis in a large sample of men undergoing clinical evaluation for hypogonadism. The association of obesity with lower SHBG was two to three times larger than the association of ageing with increased SHBG in both univariate and multivariate modelling.

On average, obese men had significantly lower SHBG and total testosterone concentrations than non-obese men, but calculated free testosterone concentrations did not differ between obese and non-obese men. The progressive decline in SHBG with increasing BMI was greater than the progressive increase in SHBG with age across all tertiles.

The authors conclude that these effects on SHBG may have an impact on the utility of total testosterone measurements in the diagnosis of low testosterone, particularly in obese men.

Read the full article in *Clinical Endocrinology* **83** 828–833

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS

Aripiprazole in microprolactinoma and cabergoline-induced mania

The utility of dopamine agonists in the treatment of prolactinoma can be limited by psychiatric side effects, including mania and psychosis. In such cases, the medication is stopped and surgery is often required.

Burback reports the case of a 32-year-old woman with an 8mm cystic microadenoma with no history of psychiatric disorders, who developed mood swings when prescribed cabergoline, and eventually acute mania with psychotic features. Cabergoline was withdrawn and the patient was treated with aripiprazole. In contrast to most antipsychotics, aripiprazole is a partial dopamine agonist. This drug successfully treated her psychotic illness, and suppressed her prolactin levels and tumour size over 18 months of follow up.

It has been used previously in risperidone-induced hyperprolactinaemia, and further investigation into its potential in the treatment of prolactinoma is advised.

Read the full article in *Endocrinology, Diabetes & Metabolism Case Reports* **11** EDM150100 (OA)

ENDOCRINE CONNECTIONS

HSP90 inhibition in differentiated thyroid cancer

Dose-limiting toxicity has restricted the use of kinase inhibitors in differentiated thyroid cancer. Gild *et al.* have taken advantage of the role of the heat shock protein HSP90 in mediating the effect of kinases such as RET, AKT and BRAF to investigate an alternative mechanism to downregulate these pathways. HSP90 regulates protein degradation of these kinases, and is overexpressed in cancer cells. The action of an HSP90 inhibitor AUY922 against medullary and papillary thyroid cancer (PTC) cell lines expressing a RET mutation was studied *in vitro*.

AUY922 inhibited MAPK and mTOR signalling and induced apoptosis *in vitro*, and enhanced radioactive iodine uptake in the PTC cell line. The latter effect is particularly significant given the reduced iodine avidity of such tumours clinically.

AUY922 is in trials for non-small cell lung cancer, and the authors propose streamlining into thyroid cancer trials.

Read the full article in *Endocrine Connections* **5** 10–19 (OA)


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Different strokes for different folks

Most people would consider themselves able to tell the difference between 'good' and 'bad' diets. However, these adjectives suggest we can assume that the variability in, say, blood glucose after eating a foodstuff is all down to the composition of what was eaten.

Zeevi *et al.* combed a range of biochemical, transcriptomic and anthropometric data to show there is a high degree of interpersonal variation in our response to food, with people eating identical meals exhibiting very different (but reproducible) post-meal blood glucose responses. Using data from subcutaneous continuous glucose monitoring, they generated a machine-learning algorithm that accurately predicted personalised glycaemic response to 'real world' meals. Using these tools in a small cohort receiving personally tailored dietary interventions, the authors could (in the short term at least) successfully lower postprandial glucose.

As well as being a powerful study in documenting the heterogeneity within the population, this work gives much food for thought about how dietary interventions for disorders of glucose homeostasis may be shaped in future.

Read the full article in *Cell* **163** 1079–1094 (OA)

Ghrelin potential as a therapeutic agent for peripheral artery disease

The therapeutic options to treat critical limb ischemia (CLI; a severe obstruction to the blood vessels that restricts blood flow to the extremities) are limited. However, recent *in vitro* studies have reported that ghrelin, a peptide hormone more commonly known for its role in appetite regulation, may also have angiogenic properties. Katare *et al.* used a mouse model of CLI to investigate whether ghrelin could promote post-ischemic angiogenesis and if so, what the mechanistic pathways underlying this were.

They found that administering ghrelin daily over a two-week period resulted in improved blood flow to affected limbs, promoted the growth of new structurally and functionally normal blood vessels, improved cell survival and decreased tissue fibrosis. Subsequent molecular analysis showed that the observed effects were likely due to the activation of proangiogenic and antifibrotic microRNAs. These results provide a platform for further studies to assess the potential of ghrelin to become a novel therapeutic agent for CLI.

Read the full article in *Endocrinology* doi:10.1210/en.2015-1799 (OA)

Immunometabolic effects of FGF21

Fibroblast growth factor 21 (FGF21) is a hormone that has come to prominence in recent years for its role in improving insulin sensitivity, and thus for its potential use as a weight-loss agent.

Youm *et al.* have used transgenic mice with elevated FGF21 levels to investigate this hormone's effect on the thymus. The thymus produces T cells, which play a central role in cell-mediated immunity. With age, the thymus has been shown to become fatty, and its ability to produce new T cells decreases. This is thought to contribute to the observed increased risk of infection and some cancers in the elderly.

The authors found that, in 'old' mice, higher FGF21 levels were correlated with reduced thymus degeneration and an improved ability to manufacture new T cells, while the opposite was observed in individuals with low FGF21 levels. This is the first description of this immunometabolic regulator role for FGF21 in the thymus, which may have important implications for our understanding of immunosenescence.

Read the full article in *Proceedings of the National Academy of Sciences of the USA* doi:10.1073/pnas.1514511113

ENTEROENDOCRINE CELLS: SENSING WHAT YOU EAT

WRITTEN BY PAUL RICHARDS

The gut is considered to be the body's largest endocrine organ, because it produces over 20 different hormones in abundance. The cells that make and release these hormones are named enteroendocrine cells (EEC). They are found scattered throughout the epithelium from the stomach to the rectum.

Over the past decade, intense efforts have been made to characterise EECs, as some of the hormones they secrete have profound effects on metabolism and appetite. One such hormone is glucagon-like peptide-1 (GLP-1), which has formed the basis of a number of treatments for diabetes and obesity. What follows is a simple overview of these therapeutically exciting cells.

NUMBER OF ENDOCRINE CELLS IN THE GUT

EECs are considered to be rare, as they only account for about 1% of all intestinal epithelial cells. Nevertheless, the surface area of intestinal epithelium is large, so 1% equates to many millions of cells, all of which are packed with hormones (Figure 1). Under a light microscope, EECs are indistinguishable from neighbouring cells, so elucidating their inner workings has historically been very difficult.

ENDOCRINE CELL TYPES AND CLASSIFICATION

Traditionally, EECs are classified according to the principal hormone they produce, on the supposition that each EEC only produces one principal hormone. This hypothesis and classification system were recently brought into question when a number of labs produced transgenic mice that allowed the purification of EECs from different areas of the intestine. The results were surprising, as individual EECs were found to contain several different hormones[1] (Figure 1) that should arise, according to the original classification, from distinct cell types.

In a recent study, researchers performed single-cell RNA sequencing on individual EECs and found many different subtypes.[2] The cellular diversity has thus proven to be complex and we do not yet have a new classification system to encompass all the recent findings.

MORPHOLOGY, STIMULI AND LOCATION

Most EECs in the intestines are open-type endocrine cells, with a base resting on the basal lamina and a cytoplasmic process extending to the gut lumen (Figure 2). At the tip of the process are microvilli that protrude into the lumen. It may be through these microvilli that the cells sense luminal nutrients. EEC stimuli are varied and include fatty acids, amino acids, monosaccharides, bile acids and bacterial metabolites.

Understanding the location, hormonal profile and subtypes of EECs is important. Postprandially, most nutrients are

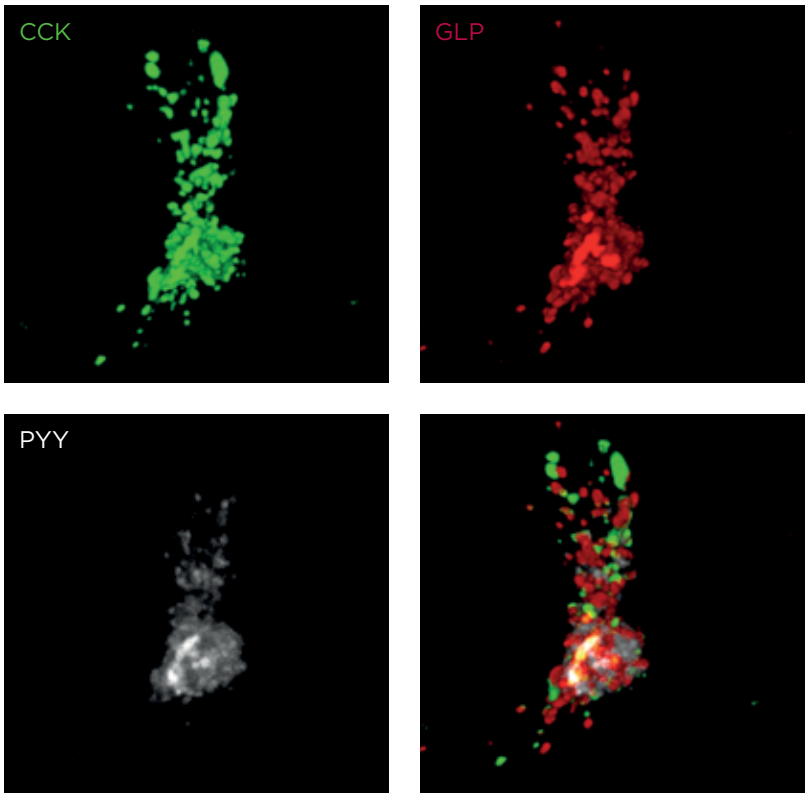

Figure 1. Immunostaining of a single EEC reveals that it contains multiple hormones: cholecystokinin (CCK, green); proglucagon-derived hormones (GLP-1/GLP-2/oxyntomodulin, red); peptide-YY (PYY, white). While the hormones appear to be in separate vesicles in this cell, we also observed cells in which the majority of vesicles stained for multiple hormones. ©Paul Richards

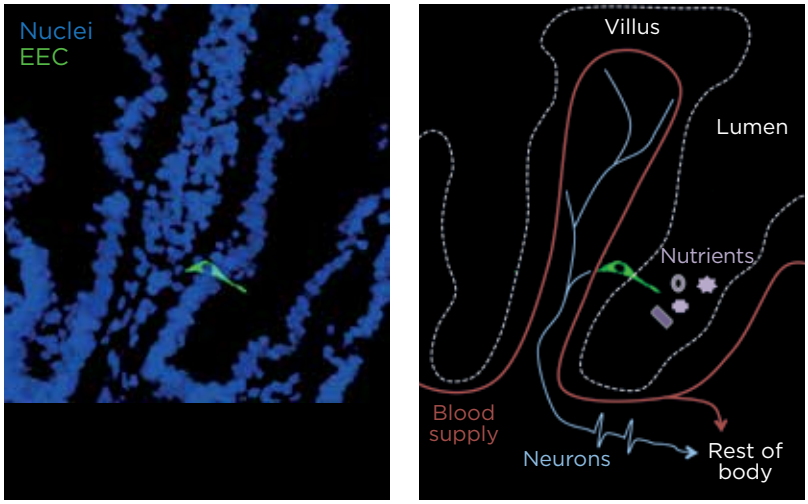

Figure 2. *Left* Immunostaining of a duodenum from a transgenic mouse for an EEC (green) and cell nuclei (Hoescht, blue). *Right* Diagram based on the image on the left, showing how the EEC may signal through the nervous (blue) and vascular systems (red). ©Paul Richards

absorbed in the duodenum and jejunum, so EECs located there will rapidly sense the digested meal and secrete hormones. Between 6 and 8 hours later, when remnants of the meal enter the large intestine, very few detectable nutrients are left. Instead, the luminal contents include indigestible fibre and microbiota. This raises the interesting question of what physiologically stimulates these most distal EECs. If it is direct luminal sensing hours after a meal, then what is the physiological role of these distally secreted hormones?

ROUTES OF SIGNALLING

In accordance with the classical definition, gut hormones can communicate with distant cells, including the pancreas and brain, via the circulation. There is a debate, however, as to whether this is the main signalling route used by all hormones secreted by EECs. An enzyme, dipeptidyl peptidase 4, which inactivates several gut peptides, is found in the capillary endothelium juxtaposing EECs. Consequently, some of the hormones have very short half-lives, which creates the suspicion that alternative signalling routes may be used. Recent reports have shown that neurones link directly via synapses to EECs[3] and express hormone receptors,[4] suggesting the tantalising possibility that they can communicate through the nervous system.

FUTURE RESEARCH

One major goal is to create drugs that will directly stimulate EECs to secrete endogenous gut hormones, thereby releasing the body's own stores of peptides that stimulate insulin secretion and reduce appetite. The use of cell lines and transgenic mice has helped us find potential target receptors on EECs, but translating these targets into medications has yet to be achieved.

To do this, a better knowledge of human EECs is required, and so techniques need to be developed to isolate and study these cells. Nevertheless, using transgenic mice and cell lines, we have already discovered many important features of EECs. And the closer we look, the more surprises we find.

PAUL RICHARDS
Postdoctoral Fellow, Institute Cochin, Paris, France

Paul Richards recently completed his PhD, under the supervision of Fiona Gribble and Frank Reimann, University of Cambridge.

REFERENCES

1. Habib AM *et al.* 2012 *Endocrinology* **153** 3054–3065.
2. Grün D *et al.* 2015 *Nature* **525** 251–255.
3. Bohórquez DV *et al.* 2015 *Journal of Clinical Investigation* **125** 782–786.
4. Richards P *et al.* 2014 *Diabetes* **63** 1224–1233.

THE MICROBIOME AND ENDOCRINOLOGY:

STRESS, SATIETY AND SOCIAL BEHAVIOUR

WRITTEN BY ROMAN M STILLING, TIMOTHY G DINAN & JOHN F CRYAN

We are living in a microbial word. This simple, easily overlooked fact is now attracting remarkable attention from diverse research fields. Most overtly, we notice our microbes in our intestines, which act as a bioreactor/fermenter housing a plethora of microbes (collectively called the microbiota or microbiome, when emphasising the organismal or genetic material respectively).

The shear numbers are humbling. According to the latest estimates, the human microbiota consists of a staggering ~100 trillion cells of at least 40,000 microbial strains in 1,800 genera, which collectively feature at least 9.9 million genes (about 500 times the number of human genes!).[1] They make up 1–2kg in an adult body, which is comparable to the weight of several human organs (Figure 1).

The microbiota not only comprises bacteria, but also archaea, protozoa, fungi, nematodes, and – most abundantly – viruses, preying on all these cells. Understanding the intricate relationships with our microbiota has swiftly become one of the most exciting areas of modern biomedicine, and targeting it promises new ways of treatment in multiple pathological conditions extending way beyond gastrointestinal disorders, from obesity to psychiatric and stress-related conditions.[2]

MICROBIAL ENDOCRINOLOGY

Mostly originating from rodent studies, the microbiota has been linked to virtually all physiological processes, including regulation of endocrine pathways in the body.[3] There is also now compelling evidence showing a strong impact of the presence and activity of certain microbes in the gut on various hormone levels affecting host physiology and behaviour.

Many studies have focused on animals raised in a sterile environment without microbiota, referred to as 'germ-free'. Using this approach, it was found that the microbiota is critical for the hypothalamic-pituitary-adrenal system and tuning the stress response at behavioural and endocrine levels. This has consequences for our understanding of stress-related psychiatric, gastrointestinal and cardiometabolic diseases.[4]

While these findings are exciting, it has to be noted that germ-free animals constitute a highly artificial model situation, which is uniquely useful to determine physiological processes influenced by the microbiota, rather than a translatable model for human disease.

Importantly, this interaction is bidirectional, with the microbiota actively recognising neuroendocrine hormones. Catecholamines have been shown to enhance growth as well as surface attachment of certain bacteria *in vitro*, and release of norepinephrine *in vivo* resulted in an increase in Gram-negative bacteria.

THE ROLE OF NEUROPEPTIDES

Another important mediator of host–microbe interaction appears to be endocrine signalling via neuropeptides. Epithelial enteroendocrine cells and enteric neurones produce neuropeptides to further transmit information on microbial components and products into the bloodstream or to the vagus nerve, which is another important relay connecting the intestines with endocrine brain centres such as the hypothalamus (Figure 2). In fact, vagotomy abolished some of the effects found in studies on mice fed with probiotics or pathogens.

Also mediated by neuropeptides, the gut microbiota has been associated with metabolic phenotypes through modulating endocrine regulation of food intake. A recent study in animal models showed that bacterial secreted proteins such as *Escherichia coli* ClpB, a mimetic of α-melanocyte-stimulating hormone, could stimulate satiety by elevating circulating levels of neuropeptide YY acting on a feedback loop in the hypothalamus.[5]

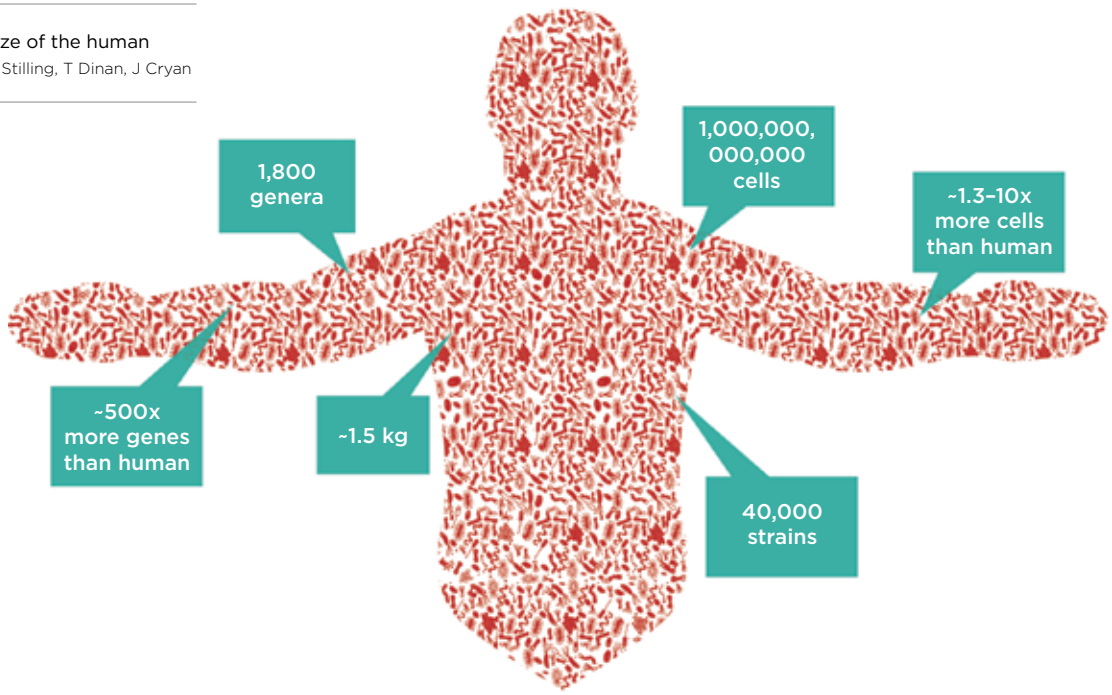

Figure 1. The size of the human microbiota. ©R Stilling, T Dinan, J Cryan

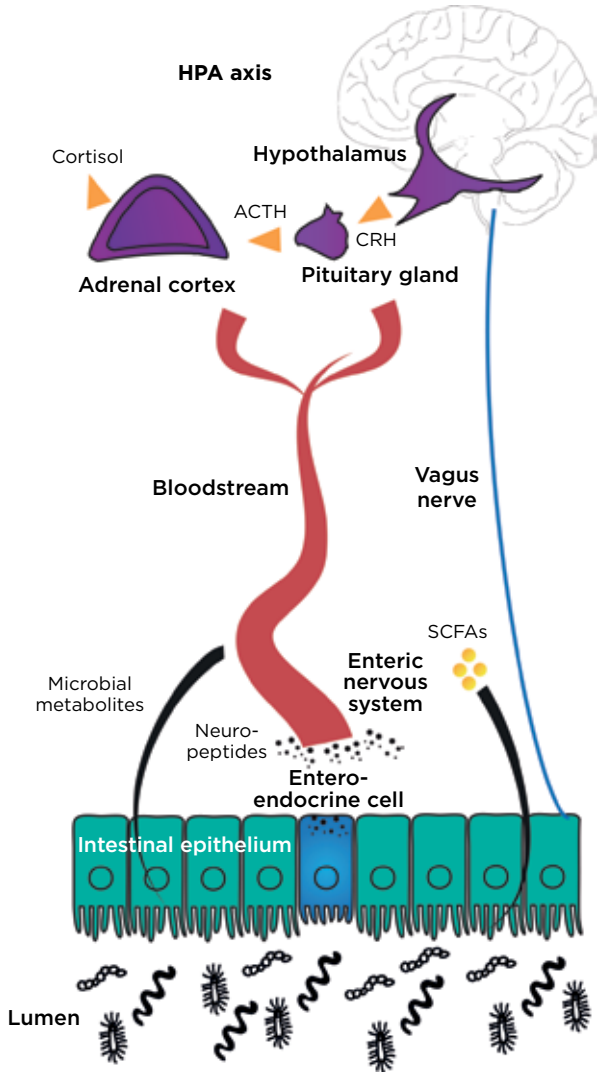

Figure 2. Communication between the microbiota and the hypothalamic-pituitary-adrenal (HPA) axis via neuropeptides. CRH, corticotrophin-releasing hormone; ACTH, adrenocorticotrophin; SCFAs, short chain fatty acids. ©R Stilling, T Dinan, J Cryan

AN IMPACT ON BEHAVIOUR

Moreover, it is becoming increasingly clear that social behaviour and disorders associated with altered sociability such as autism spectrum disorders (ASDs) are linked to the gut and microbes. These disorders are often accompanied by gastrointestinal symptoms and changes in the composition and function of the microbiota.

Interestingly, central nervous system and gastrointestinal symptoms also commonly co-occur in animal models for ASDs and seem to be dependent on host–microbe interactions.[6–8] Moreover, the neuropeptides oxytocin and vasopressin are well known for regulating social behaviour, and we have recently shown in rodent studies that this hormone system is under the control of the microbiota.[9] However, the precise mechanisms through which the gut microbiota affects change in gene expression in the brain have yet to be fully elucidated, and we await with interest further human studies.

NUTRITION AND ENERGY METABOLISM

Finally, gut microbes help to break down nutrients, which can then be used by host cells, thereby influencing host nutrition and energy metabolism. Interestingly, several metabolic by-products are associated with additional signalling functions, such as GABA (γ-aminobutyric acid) and tryptophan, as well as serotonin and dopamine, which are important neurotransmitters. Gut bacteria are also the key source of short chain fatty acids, such as butyric, propionic and acetic acids. These molecules serve as cellular energy supply as well as signalling molecules, as they are known to modulate epigenetic processes in host cells.

Together these types of mutual dependencies have led to the concept of 'microbial endocrinology'.[10]

CONCLUSIONS

A new understanding of the microbiome is on the rise. The tight evolutionary association of host and microbes has led to the 'hologenome theory of evolution' that views the host and its microbiome as one integrated unit, the holobiont.[11]

While there are also parasitic microbes that harm us, there is little reason to be worried about the intentions of the throngs of symbiotic bacteria living in our guts. In fact, to understand who we really are, it is key to understand the messages the microbes send to our body throughout development and ageing.

At the moment, the field is moving towards defining the mechanisms and pathways that specific microbes use to communicate with us. It will also be crucial to exactly identify beneficial microbial strains and metabolites, as well as to come up with new tools, such as phages and bacteria-derived bacteriotoxins, to specifically modulate the microbiome.

Finally, we need to take a whole new look at nutrition from a holobiont perspective. (Is it good for me? Is it also good for my microbiome?) Together, this will enable us to mine the microbiota and harness beneficial microbes to revolutionise drug discovery.

ROMAN M STILLING, TIMOTHY G DINAN & JOHN F CRYAN
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REFERENCES

1. Li J *et al.* 2014 *Nature Biotechnology* **32** 834–841.
2. Clarke G *et al.* 2014 *Molecular Endocrinology* **28** 1221–1238.
3. El Aidy S *et al.* 2015 *Clinical Therapeutics* **37** 954–967.
4. Dinan TG & Cryan JF 2012 *Psychoneuroendocrinology* **37** 1369–1378.
5. Breton J *et al.* 2015 *Cell Metabolism* doi:10.1016/j.cmet.2015.10.017.
6. Desbonnet L *et al.* 2014 *Molecular Psychiatry* **19** 146–148.
7. Stilling RM *et al.* 2014 *Frontiers in Cellular and Infection Microbiology* **4** 147.
8. Hsiao EY *et al.* 2013 *Cell* **155** 1451–1463.
9. Desbonnet L *et al.* 2015 *Brain, Behavior & Immunity* **48** 165–173.
10. Lyte M & Cryan JF (Eds) 2014 *Microbial Endocrinology: the Microbiota-Gut-Brain Axis in Health and Disease*. New York: Springer.
11. Bordenstein SR & Theis KR 2015 *PLoS Biology* **13** e1002226.

IMAGING OF THE BRAIN: HOW CAN IT TELL YOU WHAT YOU THINK ABOUT FOOD?

WRITTEN BY PAUL FLETCHER

Claims about what functional brain imaging tells us can be overblown, sometimes ridiculous. We are shown 'activity' (figurative representations of statistical comparisons), rendered in hot colours on structural brain images. Yellows and reds mean highly significant effects, while blues and greens are not so impressive. Then we're invited to believe that we are seeing something necessarily meaningful and informative about the highest levels of human cognition and experience: belief, morality, religion, politics. And some of the lower ones too: anger, greed and lust.

But these are, remember, statistical images, rendered into brain space. They are produced by hypothesis tests and, as in science everywhere, they are meaningless without reference to the hypothesis under examination.

Put simply, functional brain images represent the comparison of (at least) two brain states, one in which the cognitive process of interest is active and one in which it is not active (or less active). The null hypothesis being tested for a given region is that this region will show no difference in its blood oxygenation level dependent (BOLD) signal as a consequence of the process in question. A significant difference allows rejection of this null hypothesis and suggests that the region in question has some involvement in the process of interest.

Or it might not. It might simply be a bystander, activated by some unconsidered part of the task design. Or its activation might be a downstream effect of the really interesting stuff that is going on elsewhere in the brain. The confidence and precision with which we can interpret the activity difference is limited by the quality of the hypothesis and task design. Even a very expensive scanner cannot bypass this principle of science.

STICK TO YOUR HYPOTHESIS

This is not to say that functional neuroimaging can't have simple hypotheses. If I want to begin looking at cortical circuitry related to hunger-driven changes in response to food stimuli, I could design a very simple experiment in which some of my participants look at food stimuli when hungry and some of them when sated. I may try to determine whether the differences in brain response are specific to foods by using both food and non-food stimuli. I may then produce an image depicting all the areas where my null hypothesis (that hunger doesn't change the BOLD response to food stimuli) can be rejected. I now have a collection of regions that I may deem worthy of further study. A key point, however, at this stage, is that I must be wary of going beyond the inferences justified by my very simple task design (and my correspondingly very simple hypothesis).

Why am I even bothering to say this when it's so obvious? Unfortunately, there is something about functional neuroimaging that seems to make it less than obvious. Perhaps I see an increase in activation in the prefrontal cortex in my hungry participants. I know that the prefrontal cortex is associated with executive function and so I start to tell myself a story about how the hungry people were having to exert a high degree of self-control as they yearned for the food depicted in my stimuli. I like my story so much that I forget that my original hypothesis didn't actually involve self-control.

'The confidence and precision with which we can interpret the activity difference is limited by the quality of the hypothesis and task design. Even a very expensive scanner cannot bypass this principle of science.'

MRI scanner. ©Shutterstock

I also forget that nobody really yet knows precisely how the prefrontal cortex contributes to the brain's computational processing. So it may be self-control. And it may not.

INTERPRETATION AND INFERENCE

At this point, I am engaging in what has come to be known in functional neuroimaging as 'reverse inference'. I am no longer using what I know about my task design to interpret what the brain is doing; I am now using what I know about brain processing to provide a clearer description of how my task or experimental manipulation is composed. This is dangerous: partly because it is extremely bad practice to begin with a question about brain activation (which depends on claiming that I understand my experimental manipulation) and to end by claiming to know what the brain activation means and to use it to interpret my experimental conditions. It's also dangerous because we know very little at present about what brain regions actually do. Or at least, for the great majority of regions, we do not know enough to assert confidently that, if this region X is active, then the participant is definitely engaged in process Y.

So if someone tells you that she is not hungry, my advice would be to believe her, even if she is showing significant activity in brain regions that have been associated with hunger.

Is this bad news for functional neuroimaging? Only if you wish it were magic. If, on the other hand, you see it as a technique that can complement other measures at other levels, from the metabolic to the subjective, then you can remain happy. Or at least hopeful.

THE VALUE OF IMAGING

The question becomes how best to use imaging in order to test hypotheses that cannot be tested, or are only partially testable, at other levels and with other techniques. Inevitably, this will entail a slow and iterative process in which functional neuroimaging observations are used, not to pose or answer ill-specified questions (where is the hunger centre?),

'If someone tells you that she is not hungry, my advice would be to believe her, even if she is showing significant activity in brain regions that have been associated with hunger.'

but rather to converge on explanations for behaviour by attempting to establish very precise probes for well-specified cognitive processes, and to use these probes to explore the instantiation of those processes in different situations and in response to different physiological and cognitive challenges.

Imaging the brain can't tell you what you think about food. But it may begin to help characterise the collections of computations and processes (the majority of them below the level of conscious awareness) that shape how we respond to, decide about and experience food. This characterisation could offer more nuanced and sophisticated phenotypes of consumption and over-consumption, ultimately helping to shape interventions.

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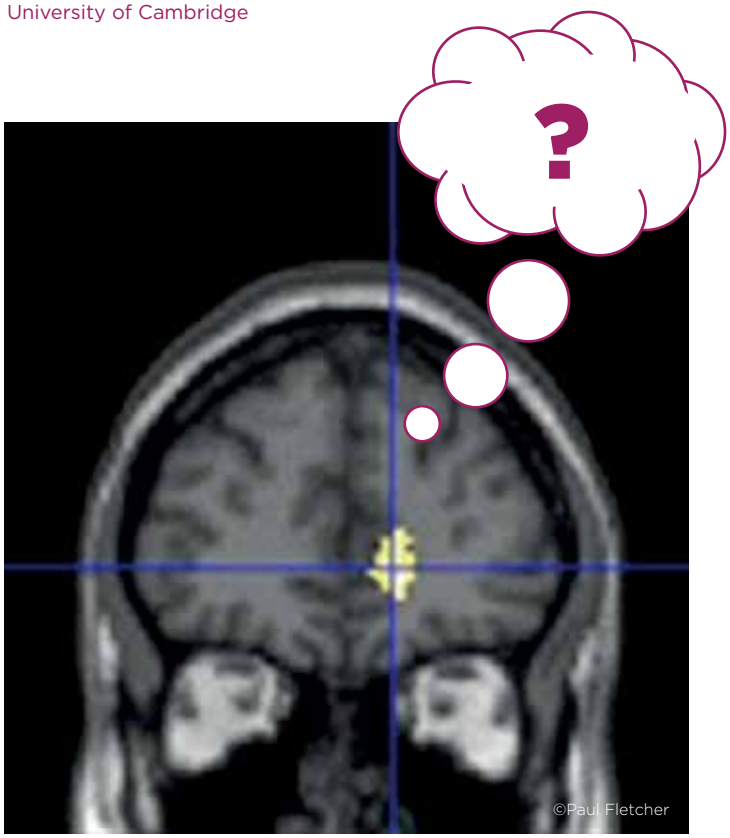

GUT FEELINGS: THE OVER-LOOKED IMPORTANCE OF HRT IN COLONIC DISEASE

WRITTEN BY PAUL FOSTER

Controversy continues to swirl around the benefits and risks associated with hormone-replacement therapy (HRT). Although experts and guidelines support short term HRT use to treat unwanted menopausal symptoms, clinicians and scientists are often confused by how HRT affects the incidence and severity of various maladies. Often over-looked are the comparatively consistent data linking HRT's effects in colonic disease and in the reduced incidence of colon cancer.

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HRT, AN OLD 'WONDER DRUG'?

Historically, prescriptions of HRTs (such as Premarin, released in the 1980s) centred on their beneficial effects in treating postmenopausal osteoporosis. Subsequent observational studies showed additional benefits, particularly with cardiovascular protection and decreased mortality, and resulted in large numbers of postmenopausal women using HRT. Thus, at the turn of the century, HRT was being hailed as a new wonder drug.

This all changed on publication of initial results from the Women's Health Initiative: randomised controlled trials designed to address, in part, how oestrogen and progestin affect morbidity and mortality in postmenopausal women. Early results, which forced the trials to be stopped and were widely publicised, indicated that HRT use increased heart disease, stroke and pulmonary embolism. However, when the data were further interrogated, these risks were less pronounced than originally thought. What did stand out was a clear protective effect of HRT on colon cancer development.

So, in light of this strong epidemiological evidence, what do we know now about HRT, in particular oestrogen, and colorectal disease? The answer is, very little. However, numerous strands of evidence are now starting to emerge suggesting HRT has an impact on many colonic diseases.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a multi-component condition characterised by heightened gut sensitivity, altered intestinal motility and impaired secretory function. It affects more females than males, with ratios reported as high as 3:1. Furthermore, women who use HRT have an increased risk of developing IBS. Despite this, few studies have characterised IBS differences between females and males. Of these, results indicate that women diagnosed with IBS report an overall lower quality of life and a greater number of symptoms, including nausea, constipation, bloating and various extracolonic symptoms (e.g. urinary urgency and muscle stiffness).

So, if IBS is worse in females, what happens when these patients hit the menopause? It has been reported that rates of occurrence of IBS among females decrease as age increases. Over 70, the incidence among females is comparable with that in males. In males, however, the occurrence of IBS is relatively constant across all age groups. Thus, the decline in incidence observed in women is related to the lowered oestrogen concentrations characteristic of the menopause. Indeed, women on HRT have double the chance of developing IBS. Unfortunately, the exact mechanisms by which oestrogens induce IBS remain to be determined, and so currently therapeutic targeting of oestrogen action in these patients remains hypothetical.

ULCERATIVE COLITIS

The largest study to explore a potential link between oestrogens and inflammatory bowel disease shows that postmenopausal women taking HRT have an increased risk of ulcerative colitis (UC). These data support various observational studies associating use of oral contraceptives, which contain oestrogen and progestin, with an increased risk of UC in premenopausal women.

Furthermore, UC risk seems to increase with the duration of oestrogen use. For example, those who take HRT for 1–5 years have a 61% increased risk compared with those who have never taken HRT. In women who have taken hormones for over a decade, the risk increases to 80%. But 5 years after stopping treatment, the risk for UC reduces, and is no longer statistically different from those who have never taken hormones.

Again, and as in the case of IBS, why HRT increases UC remains unknown. It has been suggested that oestrogen compounds modify colonic barrier function and are involved in the progression of other type 2 helper T cell-related diseases, which could explain their effect in UC.

COLORECTAL CANCER

Compared with the situations in IBS and UC, HRT's story with colorectal cancer (CRC) is more complex. Data strongly suggest that HRT is protective against CRC development. This is interesting, and somewhat counterintuitive, considering the role these hormones have in increasing development of IBS and UC – both of which are associated with increased CRC incidence. Indeed, recent evidence suggests that women with naturally higher levels of oestrogens are more than 50% less likely to develop CRC after their menopause than women with low levels.

Of even more interest is growing evidence suggesting, once CRC is formed, women taking HRT present to the clinic with a more aggressive and later stage disease. Thus, it seems possible that, whilst HRT initially protects against CRC through oestrogen signalling, an alteration in this signalling has a negative impact on patient outcome. However, significant research is needed to determine the importance of HRT and oestrogens in CRC.

Overall, it seems that HRT, and thus oestrogens, have pronounced effects on the gut and colonic disease. Understanding the underlying molecular mechanisms involved in gut oestrogenic action will most probably reveal new therapeutic avenues to treat these conditions.

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FURTHER READING

1. Murphy N *et al.* 2015 *Journal of the National Cancer Institute* **107** doi:10.1093/jnci/djv210.
2. Mulak A *et al.* 2014 *World Journal of Gastroenterology* **20** 2433–2448.
3. Khalili H *et al.* 2012 *Gastroenterology* **143** 1199–1206.

TREATING METABOLIC DISEASE WITH GUT PEPTIDES

WRITTEN BY TRICIA TAN & STEPHEN BLOOM

Gut hormones bridge the gap between gut and brain. Can they make the leap to therapy for obesity and diabetes?

With drugs such as phentermine/fenfluramine, sibutramine and rimonabant, the multi-billion dollar drug industry has been plagued by high profile failures in the medical treatment of obesity. Now the pressure is really on to find the answer for the number one health problem of the 21st century: the world pandemic of obesity and consequential type 2 diabetes.

As key components of the signalling mechanism from gut to brain, as well as regulators of metabolism, the satiety-inducing gut hormones are ideal candidates. Over 30 years of research have shown that the gut hormones regulate appetite, metabolism, gut motility, secretion, and even act as neurotransmitters (see Figure). These hormones only last minutes in the circulation, and act as the natural pathways to control the human drive to eat. Academia and industry are developing new long-acting analogues for the treatment of diabetes and obesity.

GLP-1 ANALOGUES AS A PARADIGM

First into the market, glucagon-like peptide-1 (GLP-1) analogues are now useful clinical tools for the treatment of diabetes. Exploiting GLP-1's ability to stimulate insulin secretion and reduce appetite by a central feedback effect on the hypothalamus, its analogues combine effective reductions in glycaemia with useful reductions in weight. The vanguard drugs in this class, exenatide and liraglutide, have set the scene for follower analogues in an increasingly crowded market.

To differentiate the newer analogues, the drug companies have concentrated on extending the duration of action from daily to weekly injections, e.g. exenatide LAR, dulaglutide, albiglutide and semaglutide. The most extreme example is Intarcia's ITCA 650 implanted osmotic pump, which dispenses exenatide over the span of a year. Another tactic that has been adopted by companies is to develop orally active analogues to increase patient acceptability. For example, Novo Nordisk's oral version of semaglutide has been shown in phase II trials to improve glycaemia and body weight to similar degrees to the injected version.

The indications for GLP-1 analogues have been expanded to include non-diabetic obesity. Liraglutide can achieve weight losses of 5.6kg over placebo at the higher dose of 3.0mg and, for this indication, has been approved for marketing in Europe.

PEPTIDE YY AND PANCREATIC POLYPEPTIDE ANALOGUES

All GLP-1 analogues possess dose-dependent side effects, principally nausea and vomiting, which limit their ability to suppress appetite. The

The multiple actions of gut hormones, illustrating that they are overlapping in function, and act within both the gut and the central nervous system (CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; OXM, oxyntomodulin; PP, pancreatic polypeptide; PYY, peptide YY; SST, somatostatin; VIP, vasoactive intestinal polypeptide). Images ©Shutterstock

weight losses with treatment, even at relatively high doses, are modest. Utilising other gut hormone pathways might achieve better appetite suppression with fewer side effects.

As a result, further gut hormone analogues are currently in development. For example, our laboratory has pioneered the development of analogues of peptide YY (PYY) and pancreatic polypeptide, and these are currently in phase I trials.

GLP-1 AND GLUCAGON RECEPTOR AGONISTS IN COMBINATION

One drawback with weight loss resulting from reducing food intake is that it provokes a counter-regulatory response, in that the body reduces energy expenditure. This compensates for the reduction in energy intake and limits weight loss.

Although GLP-1 analogues, as mentioned above, are able to suppress appetite, they do not increase energy expenditure. On the other hand, glucagon is well known to do both. However, it also increases glucose levels, by a small one-off release of glucose from liver glycogen and also by chronically stimulating gluconeogenesis.

By combining GLP-1 and glucagon agonist activities, it is possible to obtain a more profound suppression of food intake, together with an increase in energy expenditure, leading to a much greater weight loss than with either peptide alone. Fortunately, the GLP-1-triggered insulin release blocks hepatic gluconeogenesis, so in practice glucose control in mild diabetics is much improved.

We have shown this concept is valid using co-infusions of glucagon and GLP-1. As a result, there is now considerable interest in developing dual agonist therapy, and these are currently in phase II trials.

CONCLUSIONS

Obesity can often be solved by bariatric surgery. However, putting half of Britain through surgery, despite creating employment for surgeons, seems intrinsically undesirable, and the outcome is not adjustable or always predictable. So the need for effective and safe medical treatments is still pressing.

GLP-1 analogues have shown the way towards developing gut hormones as therapeutics, but have limited efficacy. New combinations of hormone analogues are being developed. A triple approach, combining PYY, GLP-1 and glucagon analogues, mimics what happens physiologically, and promises to deliver safe weight loss at magnitudes similar to surgery. This is the current focus of active investigation.

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NUCLEAR MEDICINE: AN IMPORTANT ROLE IN ENDOCRINOLOGY

WRITTEN BY SIRAJ YUSUF & HENRY TAM

The field of nuclear medicine is littered with eminent scientists, many of whom became Nobel laureates: Frédéric Joliot-Curie, Irène Joliot-Curie, Ernest Lawrence and Paul Dirac, to name but a few. However, nuclear medicine as the specialty we know probably would not have existed were it not for the work of Sam Seidlin on the use of iodine-131 in the treatment of metastatic thyroid cancer. It would not be an over-exaggeration to say that nuclear medicine developed to meet the needs of endocrinology.

Although armed with a wide variety of radionuclide tracers, nuclear medicine as an imaging tool is limited by the laws of physics. The radiation emitted by decaying radionuclides is prone to be scattered by other molecules in its path to the detector, causing an erroneously attenuated signal if intercepted by dense material (such as bone or metal) or a stray signal from a site with little tracer uptake. The need to wait for radionuclides to decay necessitates lengthy scans, which can be uncomfortable for some patients and makes the images susceptible to movement artefacts. The lack of anatomical details also makes accurate localisation of uptake difficult. All these factors contribute to the nickname 'unclear medicine'.

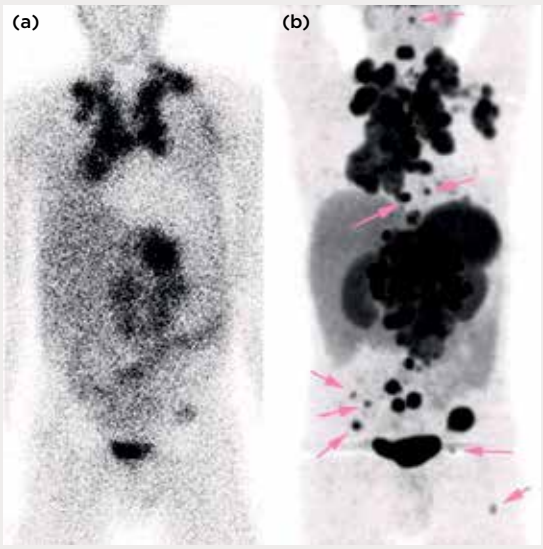
ADDRESSING THE LIMITATIONS

Thankfully, advances in computer technology have mitigated some of these pitfalls. Images acquired with a rotating camera can be reconstructed into cross-sectional images, providing localisation of the emission point in a 3D space – and so SPECT (single-photon emission computed tomography) was born. The use of statistical modelling also helps to reduce scan time, radiation dose or both. The development of tracers that used positron emission, as opposed to the traditional gamma ray (X-ray) emission, alongside the rotational camera, provided even better image quality and better localisation accuracy in the form of PET (positron emission tomography) imaging.

'The advances will hopefully usher in the era of personalised medicine that has been anticipated for the last two decades.'

Despite these, anatomical definition remained suboptimal for localisation and attenuation effects were still not totally corrected.

To address these problems, CT (computed tomography) is now performed at the same time as SPECT or PET to provide anatomical localisation and to correct for attenuation of the radioisotope emission. MRI (magnetic resonance imaging) in combination with PET imaging has recently been brought into selected clinical practice, although its actual clinical utility over PET/CT or MRI in isolation remains to be proven.



A 30-year-old male with metastatic paraganglioma. (a) Multiple ^{123}I-MIBG (metaiodobenzylguanidine) avid lesions confirmed widespread metastatic disease. (b) The same lesions were more clearly demonstrated on ^{68}Ga-DOTATATE PET/CT, which also revealed additional skeletal metastases (pink arrows). ©Siraj Yusef/Henry Tam

THE RISE OF THERANOSTICS

Nuclear medicine has been at the forefront of precision medicine with advances in theranostics, using the same ligand compound for both imaging and therapy. The ability to ablate a certain tissue type using short-ranged radioisotopes with little or no consequence to other organ systems of the body, such as iodine-131 treatment pioneered over half a century ago, is something that the rest of medicine only began to catch up on with the advent of antibody-based therapy at the beginning of the 2000s (such as Herceptin for breast cancer).

The development of functional imaging and treatment of neuroendocrine tumours, in particular gastroentericopancreatic tumours (GEP-NETs) has paralleled the development of these contemporary nuclear medicine techniques and associated tracers.

Since being first described by Siegfried Oberndorfer in 1907, this heterogeneous group of complex tumours has been poorly understood. They can have a long silent phase, until they present themselves either by mass effect or with carcinoid syndrome from metastatic disease. Although still rare, GEP-NETs have become increasingly prevalent due to an increase in investigation and diagnosis. Standard CT and MRI imaging can be relatively insensitive compared with more functional imaging techniques.

TRACER SELECTION

Targeting of the somatostatin receptor found on GEP-NETs using standard scintigraphic radiotracers such as indium-111-DTPA-octreotide is well established. However, use of higher affinity DOTA-linked somatostatin peptides (including DOTATATE, DOTANOC and DOTATOC) coupled with the PET tracer gallium-68 has provided not only a higher sensitivity and specificity, but also the higher spatial resolution and a shorter time from injection to imaging provided by PET.

Using these DOTA-linked peptides labelled with lutetium-177 or yttrium-90 rather than gallium-68, lesions that present the somatostatin receptor demonstrated on gallium-68-DOTATATE PET can be targeted for radioactive ablation. Early data for this treatment modality are promising.

New tracers working synergistically with upregulation of somatostatin receptors based on a patient's genomics or disease immunochemistry are also currently being developed. The advances will hopefully usher in the era of personalised medicine that has been anticipated for the last two decades.

Contemporary nuclear medicine and radionuclide imaging can now provide dynamic functional imaging combined with fast and accurate anatomical localisation. They can achieve a precision of treatment unrivalled by any other therapeutic options. Though still limited by the laws of physics, nuclear medicine is no longer 'unclear'.

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FURTHER READING

1. Seidlin SM *et al.* 1946 *Journal of the American Medical Association* **132** 838–847.
2. Ryodi E *et al.* 2015 *Journal of Clinical Endocrinology & Metabolism* **100** 3710–3717.
3. Kwekkeboom DJ *et al.* 2008 *Journal of Clinical Oncology* **26** 2124–2130.
4. Xu C & Zhang H 2015 *BioMed Research International* doi:10.1155/2015/917968.
5. Modlin I *et al.* 2008 *Lancet Oncology* **9** 61–72.

OBESITY SERVICES IN ENGLAND: WHERE WE ARE, AND WHERE WE NEED TO BE

WRITTEN BY NICK FINER

Despite the growing prevalence of obesity (particularly the 'tail end' made up of those with severe and complex obesity), the growing recognition of its contribution to ill health, its socio-economic cost ($16 billion in 2007), and the increasing number of effective treatments available, the provision of clinical care remains patchy and insufficient to meet the need and demand.

CURRENT RECOMMENDATIONS

It is important to recognise the background of recent revised NICE guidance on *Identification, Assessment and Management of Overweight and Obesity in Children, Young People and Adults*,[1] the recommendations of which include the following:

35. Multicomponent interventions are the treatment of choice. Ensure weight management programmes include behaviour change strategies … to increase people's physical activity levels or decrease inactivity, improve eating behaviour and the quality of the person's diet, and reduce energy intake.

73. Consider pharmacological treatment only after dietary, exercise and behavioural approaches have been started and evaluated.

92. Bariatric surgery is a treatment option for people with obesity if all of the following criteria are fulfilled:

- They have a BMI of 40kg/m^2 or more, or between 35kg/m^2 and 40kg/m^2 and other significant disease (for example, type 2 diabetes or high blood pressure) that could be improved if they lost weight…

98. … bariatric surgery is the option of choice (instead of lifestyle interventions or drug treatment) for adults with a BMI of more than 50kg/m^2 when other interventions have not been effective.

109. Offer an expedited assessment for bariatric surgery to people with a BMI of 35 or over who have recent-onset type 2 diabetes as long as they are also receiving or will receive assessment in a tier 3 service (or equivalent).

RECENT ADVANCES

The past few years have seen a significant advance in relation to bariatric surgery, in the form of the robust registry and audit activity of the British Obesity and Metabolic Surgery Society. This has confirmed that real world practice in the UK matches clinical trial results and has shown extraordinary safety, with a 30-day mortality of 0.11%.

In addition, two weight-loss drugs have been approved by the European Medicines Agency: liraglutide 3.0mg (Saxenda) and bupropion/naltrexone extended release (Mysimba). However, neither are yet available in the UK.

A TIERED APPROACH

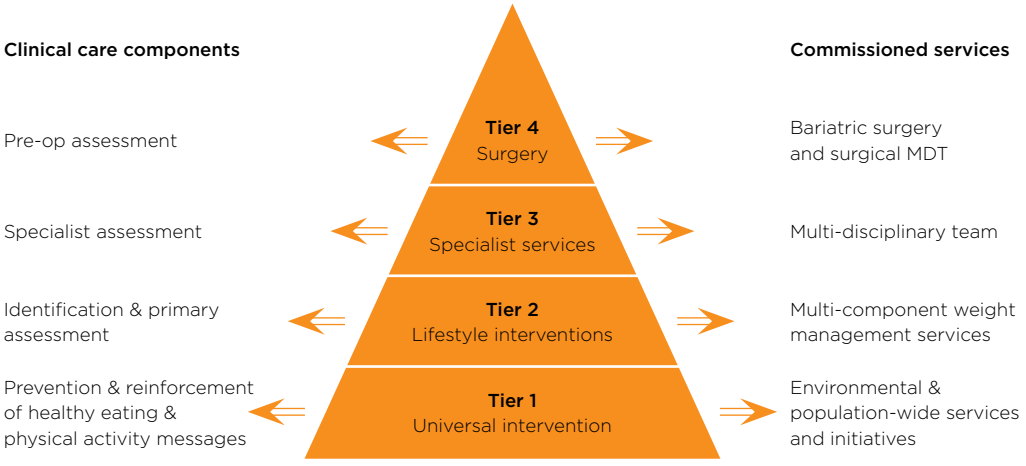
The Department of Health's strategy is based on four tiers of treatment (see Figure). Tiers 1 and 2 are funded from local authority public health budgets and relate to population prevention measures (such as Change4Life) and short term, non-medical interventions such as exercise on referral or 12-week weight loss programmes (often provided by the private sector, such as Weight Watchers).

Tier 4 services are specialist secondary care treatments mainly relating to, but not necessarily exclusively, bariatric surgery. These have been funded centrally by NHS England, but from April 2016 will be devolved to clinical commissioning groups (CCGs).

Three bodies have been attempting to ease this transition: the Clinical Reference Group on Severe and Complex Obesity (which advises NHS England), the Royal College of Physicians Obesity Working Party, and a transition group funded by industry, but with widespread representation. Surveys they have conducted show that few CCGs are either aware of the changes or have formulated any plans for taking over commissioning. In addition to the fall in number of surgical procedures performed in 2014 and 2015, many have concerns that the numbers of procedures performed will drop significantly with this lack of clarity.

According to the NICE guidance,[1] referral to tier 3 services should include those in whom:

- the underlying causes of being overweight or obese need to be assessed
- there are complex disease states or needs that cannot be managed adequately in tier 2 (e.g. the additional support needs of people with learning disabilities)
- conventional treatment has been unsuccessful
- drug treatment is being considered where BMI >50kg/m^2



Tiered approach to obesity management in England.[2] Data in this image relates to Q3 2013, with the tiers defined according to the terminology from the 2013 DoH Tier 2 guidance.[3] ©Royal College of Surgeons. Reproduced with permission

- specialist interventions (such as a very low calorie diet) may be needed
- surgery is being considered.

After a long delay, it was established that tier 3 services should be funded and commissioned by CCGs. Sadly, few have done so, and this undoubtedly has led to the fall in numbers of patients being offered or receiving weight loss surgery. The devolvement of tier 4 to CCGs does, however, offer the opportunity for joined up medical interventions leading to surgery when appropriate.

A NEED FOR CLARITY

While research into obesity causes, pathophysiology and treatment has never been more active (as a National Institute for Health Research themed call recently announced), it remains disappointing that the development of obesity medicine as a sub-specialty remains in the doldrums. This makes the career path for those clinicians with a specialist interest tortuous and uncertain.

'There is a need to develop the specialty to reflect the growing complexity of caring for those with obesity ... and to support the newer interventions such as bariatric surgery.'

Obesity medicine occupies the position held by medicine for the elderly in the 1970s. There is a need to develop the specialty to reflect the growing complexity of caring for those with obesity and its protean manifestations, and to support the newer interventions such as bariatric surgery. The establishment of the Association of Physicians Specialising in Obesity (APSO) and its growing links with the Society for Endocrinology is a welcome move forwards.

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REFERENCES

1. NICE 2014 *Clinical Guidelines* **189** [partial update of CG43] www.nice.org.uk/guidance/cg189.
2. Royal College of Surgeons *et al.* 2014 *Commissioning Guide: Weight Assessment and Management Clinics (Tier 3)* http://bit.ly/1ZbvEM5.
3. Department of Health 2013 *Developing a specification for lifestyle weight management services. Best practice guidance for tier 2 services* http://bit.ly/1PCFFqU.

EMBRACE THE PERILS OF WORKING ABROAD

FROM OUR SCIENCE COMMITTEE CORRESPONDENT

I came to Cambridge from San Francisco in 1994 to begin my PhD studies with Sydney Brenner. To be frank, it didn't begin too auspiciously. In my second week, whilst working with a Bunsen burner and an open container of ethanol, I nearly burned the lab down. But, that explosive incident aside, I enjoyed my time abroad so much that I decided to remain in Cambridge after I completed my studies in 1997 (influenced, incidentally, by my English girlfriend, who is now my wife). And 18 years on, I am still here.

When people consider working abroad, they normally think in terms of years, to obtain a PhD or train as a postdoc. But shorter visits, from a week to a few months, are equally valuable. Reasons for these range from performing an experiment, or analysing a dataset, to full-scale technology transfer, and involve individuals across the career spectrum, from students to professors on sabbatical.

Many countries, for reasons of geographical isolation, language enrichment or lack of resources, have policies in place to encourage their scientists to spend time abroad. In the not-too-distant past, this was spoken of in hushed terms as a 'brain-drain', where the USA and UK were almost imperialist in their 'poaching' of the best scientists in the world.

However, the reality today is that many who have spent time training and working abroad are now heading back to well funded positions as local scientific critical mass is built. The tangible evidence for this is the increasing number of publications with senior authors from institutions outside Western Europe and North America.

UK scientists have not had the same type of pressure to spend time away, and I'm not certain this is a good thing. Aside from aspects of training, time spent away from these isles brings a whole host of intangible benefits. These might include learning to deal with a more aggressive style of questioning in lab meetings, or perhaps honing diplomacy to ensure local technicians, often sharing little with you in terms of culture and language, help with the success of your project. These 'soft skills', when brought back to the familiarity of the UK, are invaluable as you progress through your career.

So if the opportunity arises to study or work abroad, be it for 2 weeks, 2 months or 2 years, then I say grasp it... And if it leads to marriage, a mortgage, children and a change of accent, so be it!

GILES YEO
Science Committee correspondent
Twitter: **@GilesYeo**

SOCIETY CLINICAL RESEARCH AND AUDIT PROJECTS

FROM OUR CLINICAL COMMITTEE CORRESPONDENTS

By managing five research and audit projects, the Society works towards its charitable aim to 'Advance scientific and clinical education and research in endocrinology for the public benefit'.

LONG-STANDING PROJECTS

Congenital Adrenal Hyperplasia Adult Study Executive (CaHASE) addresses clinical outcomes, quality of life and sexual function in adults with CAH. It is a highly successful model of collaboration between the Society, its members and funding from the Clinical Endocrinology Trust (CET), resulting in an impressive publication record[1] and attracting leverage funding into endocrinology. Participating centres report improved transition rates from paediatric to adult endocrine care.

In collaboration with Faisal Ahmed (Glasgow), a CAH-specific arm (i-CAH)[2] of the international registry for disorders of sexual development (i-DSD registry) has been established. As a direct result of the study, the Society is preparing guidelines on management of adults with CAH.

CaHASE is chaired by Richard Ross (Sheffield) and supported by the CET.

UK Acromegaly Register collects data on patients with acromegaly and gigantism. The project has already published on radiotherapy, surgery and medical treatment outcomes and is now looking at mortality, morbidity and incidence of secondary tumours in this patient population.

The Register is chaired by John Ayuk (Birmingham) and supported by Ipsen and the CET.

MORE RECENTLY ESTABLISHED STUDIES

Apoplexy Audit is an audit of practice and outcome. It assesses adherence to the Society's Guidelines for the Management of Pituitary Apoplexy,[3] and has completed patient recruitment (100 patients).

Apoplexy Audit is chaired by Simon Aylwin (London) and supported by the CET.

Post-Radiation Graves' Management (PRAGMA) looks at patients with Graves' disease treated with radioiodine and compares the incidence of dysthyroidism post-radioiodine between two different management strategies employed by UK clinicians. PRAGMA has successfully recruited over 800 patients from 31 UK endocrine centres and data analysis is underway for presentation at scientific meetings in 2016.

PRAGMA is chaired by Petros Perros (Newcastle upon Tyne) and supported by the CET.

Transitional Care is an audit looking at the current status of transitional care in endocrinology nationally. Initial results were presented at SfE BES 2015[4] and BSPED 2015[5].

Transitional Care is chaired by Helena Gleeson (Birmingham) and supported by the CET.

Do you have a research study that the Society could manage? If so, please contact Debbie Willis (**debbie.willis@endocrinology.org**) for further details.

NATASHA ARCHER, Clinical Projects Officer
DEBBIE WILLIS, Policy and Professional Affairs Manager

The Society thanks all involved in the success of these projects, including the financial sponsors.

FOOTNOTES

1. http://bit.ly/22TOs1R
2. www.i-cah.org
3. http://bit.ly/1mOuYdP
4. http://bit.ly/1mOv2dz
5. http://bit.ly/1K6MZcN

To get in touch with the Society's Committees, email **members@endocrinology.org**.

Metabolic and obesity ENDOCRINE NETWORK

WRITTEN BY BARBARA McGOWAN & KEVIN MURPHY

The last two decades have seen tremendous progress in our understanding of the regulation of energy homeostasis and metabolism, from precise mapping of specific neuronal circuits that regulate food intake, to identification of endocrine signals that communicate information regarding fuel reserves and nutritional status to the liver, pancreas and brain.

However, despite these advances, obesity and metabolic disease are major national and global health issues. Nearly two-thirds of UK adults are overweight or obese, and there are more than 4 million people with diabetes in the UK. The available pharmacological treatments for obesity result in relatively modest weight loss; most agents for treatment of type 2 diabetes lead to weight gain and other side effects. Bariatric surgery has impressive effects on body weight and glucose homeostasis, but is impractical to apply to the huge numbers of patients that might benefit. Much work is still required to understand the processes of metabolism and metabolic disease, and to develop new, safe and effective treatments.

It is in this context that the Society for Endocrinology has established the Metabolic and Obesity Endocrine Network. The Network aims to help such work by encouraging the cross-institutional and cross-disciplinary collaborations crucial to answering important questions. The Network should be used as a tool to facilitate partnerships between research groups. In particular, it can provide connections to make it easier to apply for grants that require, for example, large multicentre patient cohorts or diverse skill sets. Using the Network to organise specific themed meetings on particular topics will also strengthen connections between laboratories and clinical teams. The Society has made grants available for such activities: the Endocrine Network Research Grant and the Themed Scientific Meeting Grant.

The Network will act as a conduit of opinions and expertise to the Society for Endocrinology management committees to ensure that the interests of those working in metabolic disease and obesity are well represented, and that the Society responds to its members' needs in these areas. We encourage members to submit suggestions for symposia, Meet the Expert sessions and debates at the annual Society for Endocrinology BES conference, so that the disciplines associated with obesity and metabolic disease feature significantly.

As Network Leads, we are eager to hear your ideas about what the Network could do for you, whether you are a member or a potential member. We want to reflect the needs and views of the Network's wide membership, comprising basic scientists and clinicians, graduate students and professors, located nationally and internationally. The Metabolic and Obesity Endocrine Network should become a highly useful and utilised forum for those in the field. We hope that, in several years' time, members won't be able to imagine how they managed without it, and we look forward to hearing your suggestions about how we can best make this happen.

BARBARA McGOWAN & KEVIN MURPHY, Network Leads

Find out more at ***www.endocrinology.org/endocrinenetworks*** *or contact* ***debbie.willis@endocrinology.org***.

2015: The Society YEAR IN REVIEW

2 New GRANTS

Regional Clinical Cases Grant

Themed Scientific Meeting Grant

Expanded PUBLIC ENGAGEMENT

Including education events, a music festival and science cafés

28 member volunteers

4 times more people reached than in 2014

7 Endocrine NETWORKS

Around **500** members are part of our growing networks

Successful 'MERGER'

First combined Endocrine Nurse Update and Clinical Update attracted a record **53** nurse delegates

Valuable NEW GUIDELINES

on 'Assessment of atypical genitalia and sex development'

Published in *Clinical Endocrinology*, they have been cited extensively

Highest ever MEMBERSHIP

Over **2,600** members at the end of 2015

Largest increase amongst nurses and students

Updated **COMPETENCY FRAMEWORK**

Expanded guidance for adult endocrine nurses published in *Endocrine Connections*

OVER 100 Essay Prize **SUBMISSIONS**

Almost **50%** more entries for our Student Essay Prize than in 2014!

New **JOURNAL-BASED LEARNING**

20 activities from Society journals at endocrinology portal

358 registrants attracted from **74** countries

4 Society journal **SPECIAL ISSUES**

Diverse topics from '60 years of neuroendocrinology' to 'Ubiquitination and cancer'

Free to Society members!

New **STUDENT AMBASSADOR SCHEME**

32 ambassadors and endocrinology clubs now in place across UK universities

Biggest ever **SfE BES CONFERENCE**

Over **900** delegates, **97%** of whom rated the experience as good or excellent

Edinburgh GOES ENDOCRINE!

Edinburgh lived up to everyone's expectations, providing a very warm welcome as Scotland's capital hosted the 34th annual Society for Endocrinology BES conference.

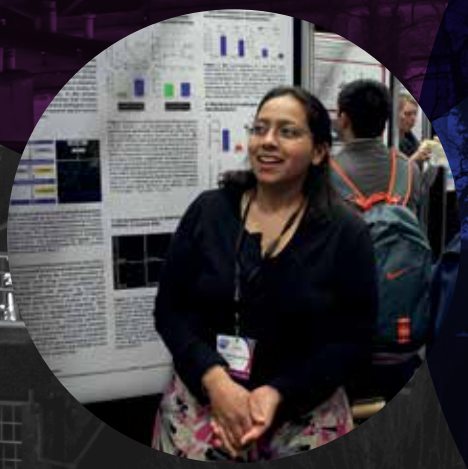
Featuring the new look 3-day format, the programme showcased the best of British and international research across the spectrum of endocrinology. Breaking all previous records, the 2015 conference was the largest to date, attracting more than 900 participants.

3 days of excellent endocrinology

905 delegates from **41** countries

71 hours of inspiring sessions, lectures and workshops

610 abstracts submitted



WHAT YOU ENJOYED...

So much breakthrough research from the field of endocrinology, all in one place!

The multidisciplinary aspect: such a range of clinical, scientific and new methods topics

Indispensable learning and networking opportunities for young trainees like myself

A great range of non-scientific sessions, like engaging with the media and the public

Talks by so many of the world's leading endocrinologists!

An excellent blend of clinical, basic and bench-to-bedside research

Educational, eye-opening, and fun!

No better platform to stay updated on current research, clinical advancements and improved practice

At least **692** news stories reported in **16** languages across **46** countries

912 visitors read the SfE BES blog

486 tweets for **#sfebes2015**

Twitter posts reached **167,600** people worldwide

World-class speakers from across the globe...

The largest meeting of endocrine professionals in the UK!

FIND MORE ONLINE

You can get the latest Society events and training information at: **www.endocrinology.org/meetings**

SAVE THE DATE

Society for Endocrinology BES 2016
Brighton, UK, 7–9 November 2016
www.endocrinology.org/meetings/2016/sfebes2016

Website
UNDER DEVELOPMENT...

The Society's new website is on its way, with improved navigation, additional functionality and a fresh new look. Thanks to everyone who has helped shape its development to date. If you haven't yet been involved but would like to help us with user testing during spring, please email **laura.udakis@endocrinology.org**.

Public engagement grants:
IS SCIENCE FOR ME?

Matthew Simmonds and Katharine Owen at the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) were recent recipients of one of the Society's Public Engagement Grants. It enabled them to run a sixth form careers event in October 2015 entitled 'Is science for me?'

Matthew and Katharine explained, 'We were really keen to create an event aimed at encouraging the next generation of scientists, medics and nurses to enter the fields of endocrinology and diabetes. We welcomed over 40 students and their teachers from 10 different schools across Oxfordshire during the day at OCDEM. They experienced lab tours, and visited a series of 12 stalls focusing on translational research, a day in the life of a researcher, laboratory techniques and commercialising research and spin off companies.'

HOW THE STUDENTS BENEFITED:

- They were full of questions and enjoyed spending time with actual scientists, medics and nurses
- They took home a pack of career resources, including the career journeys of some of the OCDEM staff.

HOW WE BENEFITED:

- We demonstrated leadership and management skills within the department – important when applying for promotions within the university
- We proved our commitment to public outreach, which is a key component of future fellowship/grant applications to expand our different research strands within OCDEM.

The next deadline for applying for a Society Public Engagement Grant is 31 March 2016. See **www.endocrinology.org/grants** for details.

70 glorious years: CELEBRATING AN EVENTFUL PAST AND AN EXCITING FUTURE

As the Society for Endocrinology marks its 70th anniversary in 2016, some of our long-standing members reflect on their personal experiences of the organisation.

Congratulations to the Society on its 70th birthday!

I'm slightly dismayed to realise that I've been an active member of the Society for almost half of its life, and more than half of mine, since having a poster at the first BES meeting in 1982. The Society has formed a big part of my working life, and I've taken part in all but one of the annual BES meetings and have also taken part in most of the available Society committees.

I have personally benefited and learned a huge amount from all the support given by the Society to both basic science and clinical practice. It was my great privilege to be Editor of *Journal of Endocrinology* a few years ago, and a pleasure to work closely with Adrian Clark who took over from me. I'm proud to have been a part of such a vibrant and professional organisation, which is now well and truly venerable!

JULIAN DAVIS, PROFESSOR OF MEDICINE AND VICE-DEAN, UNIVERSITY OF MANCHESTER
Editor-in-Chief, *Journal of Endocrinology*, 2005–2008

I'm extremely pleased with the work that the Society has done with the Addison's Disease Self Help Group. For example, the promotion of proper guidelines for surgical treatment and enabling paramedics to give hydrocortisone have been particularly important. Also, visiting different departments was an idea that I had when I was Chair of the Clinical Committee. This has ably been enacted by John Bevan and Petros Perros.

JOHN WASS, PROFESSOR OF ENDOCRINOLOGY, UNIVERSITY OF OXFORD
Chairman, Society for Endocrinology, 2005–2008

I shall always treasure my experiences at Society meetings at the Zoo and the Middlesex when I was a PhD student and postdoc. By today's standards, those meetings might sound dull – no posters, no parallel sessions and only the occasional symposium. But the lecture theatre was always packed and the audience invariably included many leading endocrinologists ready to ask probing questions well beyond their specialist research area.

I remember being absolutely terrified when I gave my first oral communication, but I soon realised that it was a wonderful learning experience. I shall always be grateful to those endocrinologists who provided such an intellectually stimulating and supportive environment. And, of course, it was at these meetings that I first met many of the friends and colleagues I have had the pleasure and privilege to work alongside for most of my career.

JULIA BUCKINGHAM, VICE-CHANCELLOR, BRUNEL UNIVERSITY LONDON
President, Society for Endocrinology, 2009–2012

MILESTONES

1930s–1940s

1939
'Journal of Endocrinology Ltd' formed
Ten guarantors pledged £40 each to support publication of a new journal. The first issue of *Journal of Endocrinology* was published on 1 July

1946
Society for Endocrinology founded
At the first AGM on 24 July, the inaugural address was 'The Scientific Foundations of Endocrinology'

1980s–1990s

1982
1st Meeting of the British Endocrine Societies (BES)
Members of the Society and other affiliated groups met in London on 25–27 May

1988
***Journal of Molecular Endocrinology* first published**
As the first editorial explained 'The expansion of our knowledge of molecular mechanisms ... is having a major impact upon endocrinology at all levels'

1994
***Endocrine-Related Cancer* first published**
Its purpose then (as now) was to provide 'An international forum for basic, clinical and experimental investigations into endocrine-related cancers'

2000s–2010s

2007
Membership database launched
The launch of a new system in September enabled the Society to process its own memberships

2012
***Endocrine Connections* launched**
The Society published its first Open Access journal, focusing on papers that examine how endocrinology intersects with other disciplines

2016
Society celebrates 70 successful years
Journal of Endocrinology reaches volume 228
The 35th Society for Endocrinology BES conference will take place in Brighton on 7–9 November

Your essential reading list: JOURNAL HIGHLIGHTS OF 2015

As a member of the Society for Endocrinology, remember to take advantage of your free online access to Society journals. It's not too late to discover the rich source of knowledge within 2015's journal content!

JOURNAL OF ENDOCRINOLOGY: CELEBRATING 60 YEARS OF NEUROENDOCRINOLOGY

August's special anniversary issue, guest-edited by Ashley Grossman and Clive Coen, marked 60 years since Geoffrey Harris first presented evidence for the functional link between the endocrine and nervous systems. It features research and reviews on many areas of neuroendocrinology, including the neuroendocrine hypothalamus, glucocorticoid dynamics, the hypothalamo-pituitary-gonadal axis, acromegaly and craniopharyngioma. You can also enjoy memoirs written by peers of Geoffrey Harris: Seymour Reichlin, George Fink and Geoffrey Raisman.

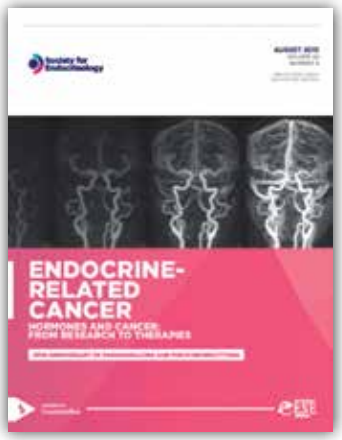
Journal of Endocrinology 2015 **226(2)** http://bit.ly/JOEthemedissue

ENDOCRINE-RELATED CANCER

'Ubiquitination and cancer' was the theme of February's special issue, guest-edited by Deborah J Marsh. Her editorial on 'Networks regulating ubiquitin and ubiquitin-like proteins promise new therapeutic targets' is accompanied by four free-to-read thematic reviews on: the ubiquitin-proteasome system, histone H2B monoubiquitination, deubiquitinases and regulation of cancer-related pathways.

Endocrine-Related Cancer 2015 **22** E1–E3, T1–T70 http://bit.ly/1SwLkSF

'15 years of paraganglioma' was the subject of August's special issue, guest-edited by Hartmut PH Neumann and Wouter de Herder. Their editorial examined 'Energy and metabolic alterations in predisposition to phaeochromocytomas and paragangliomas: the so-called Warburg (and more) effect, 15 years on'. The issue includes seven free-to-read reviews on genetics, metabolism, clinical manifestations, pathology, imaging and a historical perspective on genetic syndromes.



Endocrine-Related Cancer 2015 **22** E5–E7, T71–T159 http://bit.ly/1LOfOdi

'Stem cells and cancer' was guest-edited by Dean G Tang for the December special issue. His editorial, 'Cancers of the breast and prostate: a stem cell perspective', is accompanied by five free-to-read thematic reviews on the mammary stem cell hierarchy, the role of steroid hormones in breast cancer, mechanisms of prostate cancer initiation, genetically engineered mouse models of prostate cancer and androgen receptor and prostate cancer stem cells.

Endocrine-Related Cancer 2015 **22** E9–E11, T161–T220 http://bit.ly/21vmSqJ

JOURNAL OF MOLECULAR ENDOCRINOLOGY: CELEBRATING 75 YEARS OF OESTRADIOL

Evan Simpson (left) and Richard J Santen (right) compiled a thematic review for the December issue on the background to Edward Doisy's discovery of oestradiol in 1940. Doisy's success was the culmination of studies which began with the purification and crystallisation of oestrone in 1929. The review also includes a summary of current understanding of the biosynthesis of oestrogens, details of their molecular mechanisms of action and disorders characterised by oestrogen insufficiency.

Journal of Molecular Endocrinology 2015 **55** T1–T20 http://bit.ly/1Q0PhkB

ENDOCRINOLOGY, DIABETES & METABOLISM CASE REPORTS: THE READERS' FAVOURITE

Towards the end of 2015, users of this Society for Endocrinology-endorsed database were asked to vote for their favourite from the first 100 published cases. 'One year remission of type 1 diabetes mellitus in a patient treated with sitagliptin' by Marcos M Lima-Martinez *et al.* won the readers' vote.

Endocrinology, Diabetes & Metabolism Case Reports 2014 **9** EDM140072 http://bit.ly/1O3QhP7

ENDOCRINE CONNECTIONS

'Interacting disciplines: cardiac natriuretic peptides and obesity' is an open access special review. Here, Hugo R Ramos, Andreas L Birkenfeld and Adolfo J de Bold consider the perspectives of both an endocrinologist and a cardiologist.

Endocrine Connections **2015 4 R25–R36 http://bit.ly/1SwM6PE**

'The heart as an endocrine organ', written by Tsuneo Ogawa and Adolfo J de Bold, explores the evidence demonstrating that populations of heart cells have a partly endocrine phenotype, in an open access special review.

Endocrine Connections **2014 3 R31–R44 http://bit.ly/1YI3JzL**

OPEN ACCESS PUBLICATION DISCOUNTS

Don't forget! Society members are entitled to the following reductions in open access article publication charges:

- a 10% discount for *Endocrine Connections*
- a 20% discount for *Endocrinology, Diabetes & Metabolism Case Reports*

HIGHLIGHTS IN 2016

Watch out for special issues of Society journals in 2016:

- *Journal of Molecular Endocrinology*: 60 years of POMC
- *Endocrine-Related Cancer:* Women in endocrine cancer; 20 years since the discovery of the link between BRCA2 and cancer risk

SOCIETY MEMBERS

Take advantage of your free access to the Society's subscription journals. Log in at **www.endocrinology.org/members**

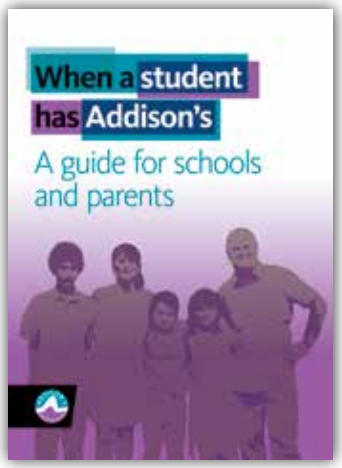
SOCIETY SESSION AT MENOPAUSE MEETING

The Society for Endocrinology is running a joint session with the British Menopause Society at their annual conference on Friday 20 May 2016 at the Royal College of Physicians in London. More information is available at **http://bit.ly/1TX6XMC** or from **admin@bms-whc.org.uk**.

UK THYROID TEAM WIN TOP HONOURS

TEAMeD (Thyroid Eye Disease Amsterdam Declaration Implementation Group UK) has won a major award for their work on improving outcomes for patients with thyroid eye disease (TED) through prevention, early diagnosis and early intervention.

They won the Judges' Special Award at the Bayer Ophthalmology Honours Ceremony, which identifies exceptional initiatives that show clinical excellence and innovation in ophthalmology. The initiatives implemented by TEAMeD include publishing national guidelines on assessing and managing patients with TED, developing an online anti-smoking tool advising patients with TED of the risks and developing a new diagnostic tool to identify undiagnosed patients. You can learn more about the project at **www.btf-thyroid.org/projects/teamed**.



NEW SCHOOLS' GUIDE ON ADRENAL INSUFFICIENCY

The Addison's Disease Self Help Group (ADSHG) has published a new guide for schools and parents on how to manage adrenal insufficiency in children when they are at school. The guide is designed for school staff, to ensure they understand the nature of steroid dependence, with practical suggestions on how to support students in managing their condition. The guide is free to download from the ADSHG website at **www.addisons.org.uk/schools**.

EVELYN ASHLEY SMITH AWARDS

The British Thyroid Foundation invites applications from nurses, endocrine nurses, midwives and healthcare professionals with a special interest in thyroid disorders. These awards are made possible by the late Evelyn Ashley Smith, for many years a member of the BTF. The £1,000 award can be used to support a specific project lasting one year or an ongoing project. The £500 award can be used to support training needs and travel expenses or conference registration fees and travel expenses. Visit **www.btf-thyroid.org** for an application form. The closing date for applications is 1 July 2016.

IN PURSUIT OF A RESEARCH FELLOWSHIP ABROAD

WRITTEN BY MARK HANNON

The specialist training programme should be an enjoyable journey, not a tiresome steeplechase in which all eyes are focused on the finishing line of an NHS consultant post. However, many young trainees work so hard in the early part of their specialist training programme that they may forget to stand back to take a critical look at their long term career path, and what they hope to gain from the journey itself. Many of the doctors who leave specialist training before completion cite fatigue and 'burn out' as major contributors to their decision to quit.

As a recently appointed consultant who pursued a 1-year research fellowship in the USA during the course of my training before returning to work in the UK, I firmly believe that a fellowship abroad can broaden the mind, reignite one's interest in the specialty, and open up previously unthought-of opportunities.

I finished my undergraduate degree in 2004 at University College Cork, Ireland, and entered the Irish Specialist Training Programme in Endocrinology in 2007. I undertook my MD research with Professor Chris Thompson at Beaumont Hospital, Dublin, examining the aetiology of hyponatraemia following traumatic brain injury and subarachnoid haemorrhage.

At the time, my only aim was successful completion of my research. However, as I read more widely on this topic, I found that a huge number of the keynote papers in this area were being written by Professor Joe Verbalis, of Georgetown University, Washington, DC, USA. Through Professor Thompson, I was able to meet Professor Verbalis at the Endocrine Society's annual meeting in the USA. He was delighted to meet an overseas trainee with an interest in his specialist subject. Thankfully, I obtained an educational grant from the Irish Endocrine Society which enabled me to work with Professor Verbalis for an academic year in his lab, while at the same time being exposed to an entirely different healthcare system and ethos.

'Many young trainees work so hard that they may forget to stand back to look at their long term career path, and what they hope to gain from the journey itself.'

Based upon my experience, here are some key tips to help get your plans to travel off the ground:

1. Once you have an area of interest within the specialty, read widely around this topic. Try to make time to look at overseas literature as well as UK publications. You will almost certainly be surprised at the diverse range of specialists working in your area of interest. Doctors are overwhelmingly collegiate – they will be glad to hear from a new person interested in the same field as themselves.
2. Attend as many overseas meetings as possible. The annual meetings of the European Society of Endocrinology and the Endocrine Society in the USA are excellent opportunities to see how endocrinology works in different parts of the world, hear alternative points of view, and have a fun trip to a foreign destination!
3. Maintain your membership of the various endocrinology societies, particularly the Society for Endocrinology. Funding for short trips to conferences or longer overseas research secondments is hard to come by in the current economic climate, but there are more grants available than trainees are sometimes aware of. Stay informed!
4. Talk to your professional training body in the UK early. Although generally very supportive of trainees travelling abroad to work for a period of time, they will want to know what you intend to do and what your long term plan is. The sooner you set this conversation in motion the better.
5. Be aware of the restrictions governing the practice of foreign physicians in your chosen destination. This particularly applies to the USA. It is currently extremely difficult to transfer from a UK or Irish specialist training programme to a US clinical fellowship programme, which is why my year in Washington, DC, was primarily a research fellowship with limited clinical involvement (though I did get some useful clinical exposure thanks to my ever-helpful US colleagues). It's very important to be aware of what you will (and won't) be able to do when working in a foreign health service.
6. The same advice applies to immigration law. For the USA, one must have a firm job offer before applying for a temporary residence visa, which is a convoluted and slow process. Get things moving early!
7. Many UK and Irish graduates limit their ambitions to other English speaking countries, but freedom of travel and employment across the EU offers a huge range of opportunities to the ambitious trainee. Some of the larger tertiary centres in the EU, particularly in northern Europe, conduct their research work though English. However, maintaining one's language skills makes one a far more attractive employment prospect.

Lastly, I would say keep an open mind! Thanks to modern communications and transport, it has never been easier to see the world and add to your CV into the bargain.

MARK HANNON
Consultant Endocrinologist and Physician,
Bantry General Hospital, Cork, Ireland

ENDOCRINE SPECIALIST NURSES AND NURSE-LED CLINICS: A UK PERSPECTIVE

WRITTEN BY LISA SHEPHERD

Whilst preparing for the Society for Endocrinology BES conference 2015, it became apparent there were few data regarding nurses running nurse-led clinics in endocrinology.

Development of nurse-led clinics has been driven by a number of factors in the NHS, including increased health needs, cost, health policy, and the reduction in junior doctors' hours. Nurse-led clinics are now embedded into specialist nursing care, and typically focus on chronic disease management, where regular follow-up and expertise are required, but also where a patient may not necessarily need to see doctor at every visit.

However, nurse-led clinics in endocrinology have been comparatively slow to evolve.

We therefore took preliminary steps to better understand the situation in the UK. Dr Helen Turner, Mrs Anne Marland and Dr Rachel Austin helped to compose questions for a survey covering:

- the roles undertaken by endocrine specialist nurses
- the knowledge, skills and training required
- the types of clinics provided
- the impetus for and barriers to these services
- service evaluation
- any medico-legal issues encountered

'Nurse-led clinics in endocrinology have been comparatively slow to evolve.'

The questionnaire consisted of 35 multiple choice and open response questions. The Society for Endocrinology distributed the survey electronically to Nurse members; 50% of recipients (n=45) responded.

In summary, the responses revealed that:

- 84.4% of nurses run clinics, in a wide range of specialisms
- thyroid clinics are performed by nurses most frequently, followed by dynamic function testing, growth hormone replacement and hypogonadism management
- nurses see large numbers of patients: 42.5% see >50 patients per month and 10% review >150 patients per month
- there is a high level of autonomy in practice: 81% optimised or changed medications; however, 50% were not medical prescribers.

Whilst nurses provide a varied and valuable service, the training, development and experience required to run nurse-led clinics are not formalised. The Society for Endocrinology's Competency Framework for Adult Endocrine Nursing,[1] and the MSc work-based learning module in collaboration with Oxford Brookes University (see *The Endocrinologist* issue 118), can assist with this. Highlighting the benefits of nurse-led clinics to Trusts and colleagues would aid their implementation and overcome the barriers to their inception. Experienced nurses should serve as role models to colleagues who wish to establish nurse-led clinics.

Dissemination of these findings is important for nursing practice, and an initial presentation took place at the Society for Endocrinology BES conference 2015 in November.[2] A further abstract has been submitted to ENDO 2016, which highlights results regarding the knowledge and skills required to provide nurse-led specialist endocrine clinics. This will stimulate international perspectives and wider collaboration with our colleagues.

LISA SHEPHERD
Nurse Committee Chair, Society for Endocrinology

REFERENCES

1. Kieffer V *et al.* 2015 *Endocrine Connections* **4** W1–W17.
2. Shepherd L *et al.* 2015 *Endocrine Abstracts* **38** P176.

LISA SHEPHERD

NURSE COMMITTEE CHAIR

Hopefully, I'm not too late in wishing you all a happy 2016! This issue features me twice, for which I apologise. However, I hope you find the results of the survey discussed in the article above as interesting as I did. The findings highlight the importance of nurses in the running and development of nurse-led clinics.

We are always looking for articles from nurses on anything you wish to share from practice, research or attendance at meetings. These could include such things as interesting cases, development of new services, or how new guidelines have been implemented or audited.

Dissemination is a fundamental part of nursing practice, promoting and raising standards. At some point, most of us have been involved in 'reinventing the wheel'. For example, after hours of working on a patient information leaflet or a protocol, we find that if we had only asked one of our nurse colleagues, we could have used one they had already prepared.

So I look forward to future article submissions from you. Remember, what you may think is not of interest to other endocrine nurses could actually be the very thing they have been looking for.

I hope to see you all in Birmingham at Endocrine Nurse Update 2016 on 21–22 March. See **www.endocrinology.org/meetings** for more information and online registration.

LISA SHEPHERD

SUPPORTING THE SUPPORTERS: HOW A SOCIETY GRANT BOOSTED THE BTF

WRITTEN BY JULIA PRIESTLY

One of the strengths of a small charity like the British Thyroid Foundation (BTF) is the network of wonderful volunteers we have, throughout the UK, who work hard to provide reliable information and peer support to people with thyroid disorders and their families.

Since the BTF was established in 1991, dozens of volunteer-run local groups have provided an invaluable resource to patients. There are currently seven thriving local groups, as well as 16 volunteer telephone contacts, who take calls and offer guidance and support based on their own experiences.

Between them, the volunteers are in contact with hundreds of patients each year. The BTF takes seriously its responsibility to ensure that they are equipped to perform their role as effectively and safely as possible. We were therefore delighted to receive a Society for Endocrinology Patient Support Grant in 2014 to use for specialist listening skills training, that would improve the service the charity offers.

A VALUABLE EXPERIENCE

The training took place over a sunny weekend in June, when 14 of our volunteers gathered in York for the 1-day professional training course, which covered all aspects of listening skills. These included sessions on active listening, reflection, paraphrasing and summarising, empathy and empathic responses, types of questions, questions to avoid, open questions, giving feedback, non-verbal communication and barriers to communication.

Throughout the day there were opportunities for participants to ask questions and for discussion of how the skills related to their roles: in particular, dealing with difficult callers, ending a call and the importance of creating boundaries.

On the following day, we held a half-day training update for local co-ordinators, where volunteers had the chance to share ideas and suggestions about running their groups, fundraising and raising the profile of thyroid disorders and the BTF.

MANY BENEFITS FOR THE BTF

The volunteers who took part in the event all agreed that it was invaluable to their role to have had this training opportunity.

- The meeting was an excellent chance to share best practice and to foster a stronger community

- BTF staff benefited from meeting volunteers as a group and learning how to improve the support they are given
- Volunteers will use the new skills when speaking to patients and at local meetings where they represent the BTF
- Sharing suggestions for maximising fundraising opportunities, and raising awareness about support, will help the sustainability of the BTF and improve its service.

FANTASTIC FEEDBACK

The feedback we received was overwhelmingly positive. As one participant remarked, 'Just to say what a useful event Saturday was and very empowering, I got a lot out of it. Thanks once again, really fantastic.'

The trainer was also very impressed with the dedication of the volunteers. 'I really enjoyed training with your group of volunteers. They are inspirational in what they do and in sharing their stories.'

WHY IT MATTERS

Keeping in touch with volunteers who represent an organisation and ensuring that they are properly supported are ongoing responsibilities for all charities. Ideally, training events should take place regularly and in different parts of the country, to make sure they are accessible to as many volunteers as possible. In order to nurture and retain our volunteers, it is essential that we keep in touch with them regularly and continue to seek their views and feedback.

The York event was a fantastic opportunity for us to appreciate how much the volunteers do and how responsibly they go about representing the BTF. It was also an important reminder of the enormous value of training events and how much we all learn by listening to the experiences of patients and volunteers.

We thank the Society for Endocrinology for awarding us the Patient Support Grant and enabling this event to happen.

JULIA PRIESTLY
Development Officer, British Thyroid Foundation

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Twitter:	**@britishthyroid**
YouTube:	**www.youtube.com/BTFThyroid**

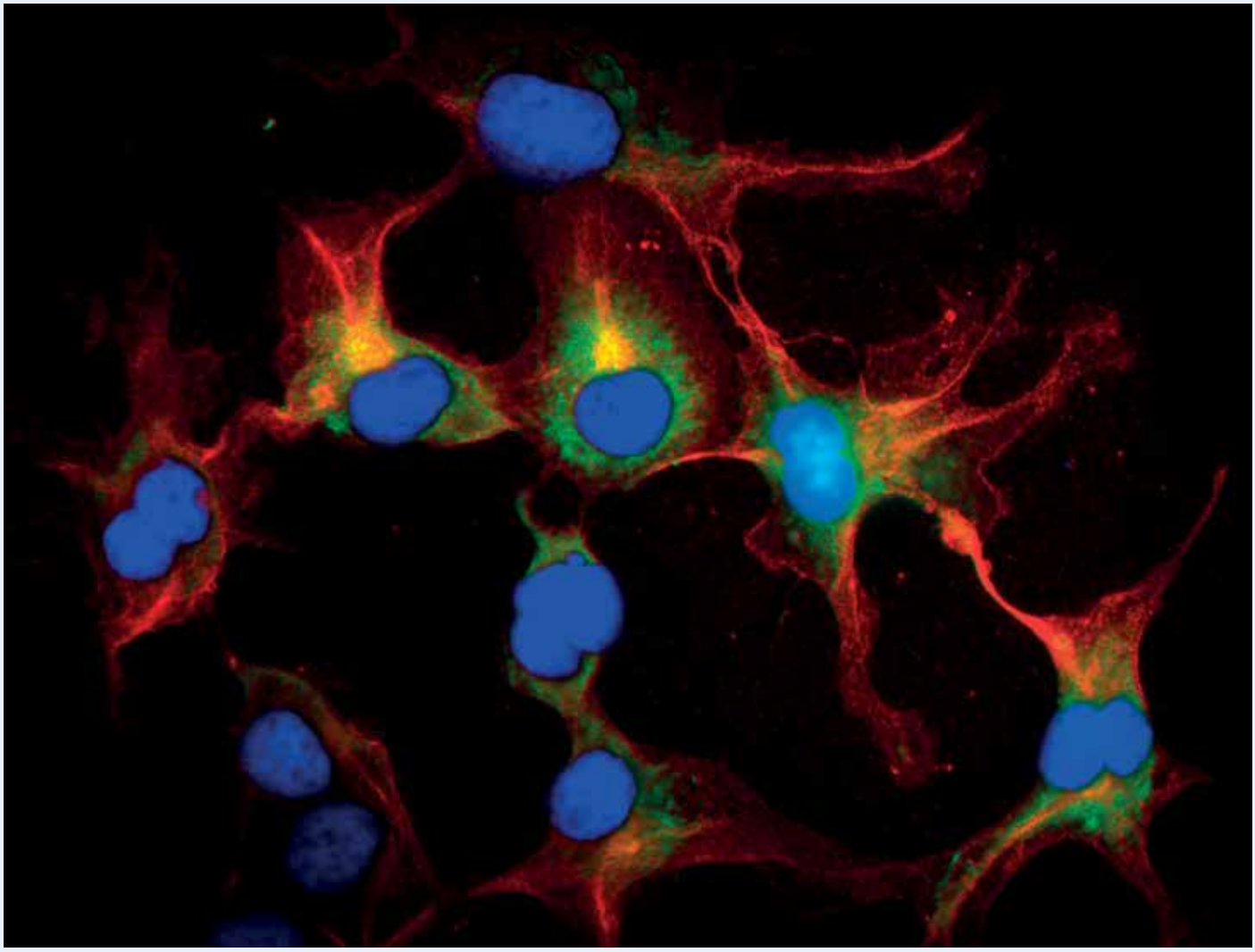
Images in ENDOCRINOLOGY

Here is the latest highlight from our journal Cover Art Competition, showcasing the best images in endocrinology.

COVER IMAGE FROM *JOURNAL OF ENDOCRINOLOGY*

JANUARY 2016

Co-localisation of *Slc12a1* and *Slc12a2* in COS7 cells treated with bumetanide. FITC (green)- and Cy3 (red)-conjugated secondary antibodies were used to label *Slc12a2* and *Slc12a1*, respectively. Cell nuclei were counterstained using DAPI (blue). (Alshahrani S *et al.* 2015 *Journal of Endocrinology* **227** 153–165.) *Credit: S Alshahrani, Wright State University, Dayton, OH, USA.*



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Presentation: Tostran 2% Gel, contains testosterone, 20 mg/g. **Indication:** Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests. **Dose:** The starting dose is 3 g gel (60 mg testosterone) applied once daily to clean, dry, intact skin, on the abdomen or to both inner thighs. Adjust dose according to clinical and laboratory responses. Do not exceed 4 g of gel (80 mg testosterone) daily. Apply after washing, bathing or showering. Do not apply to the genitals. Do not use in women, or children under the age of 18 years. **Contraindications:** Known or suspected carcinoma of the breast or the prostate. Hypersensitivity to any of the ingredients. **Special warnings and precautions for use:** Not to be used to treat non-specific symptoms suggestive of hypogonadism if testosterone deficiency has not been demonstrated and if other aetiologies have not been excluded. Not indicated for treatment of male sterility or impotence. Monitor testosterone at regular intervals. Adjust dose to maintain eugonadal testosterone level. Experience in patients over 65 years is limited, account for lower serum testosterone with increasing age. Pre-examine all patients to exclude a risk of pre-existing prostatic cancer. Perform regular monitoring of breast and prostate. Androgens may accelerate the development of subclinical prostatic cancer and benign prostatic hyperplasia. Monitor haemoglobin, and haematocrit, liver function tests and lipid profile during long-term use. Oedema with/without congestive heart failure may be a severe complication in patients with pre-existing severe cardiac, renal, or hepatic insufficiency, or ischaemic heart disease. Discontinue immediately if such complications occur. Use with caution in hypertension, epilepsy, migraine and sleep apnoea as these conditions may be aggravated. Care should be taken with skeletal metastases due to risk of hypercalcaemia/hypercalciuria. Androgen treatment may result in improved insulin sensitivity. Inform the patient about the risk of testosterone transfer and give safety instructions. Health professionals/carers should use disposable gloves resistant to alcohols. **Interactions:** Androgens can increase the anticoagulant effect of anticoagulants. Concurrent administration with ACTH or corticosteroids may increase the likelihood of oedema. **Side-effects:** Very common: Application site reactions (including paraesthesia, xerosis, pruritis, rash or erythema). Common: Increased haemoglobin, red blood cell count, and haematocrit. Increased male pattern hair distribution. Hypertension, gynaecomastia, peripheral oedema, and increased PSA. May cause irritation and dry skin. Consult SPC for further details of side-effects. **Pack Size and Price:** Packs containing one or three 60 g metered-dose canisters per pack. Price £28.67 per canister. **Legal Category:** POM. **Marketing Authorisation Holder:** ProStrakan Limited, Galabank Business Park, Galashiels, TD1 1QH, UK. Marketing Authorisation Number: PL 16508/0025 ©ProStrakan. ® Registered Trade Mark.
Date of PI Preparation: October 2015.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to ProStrakan Ltd on 01896 664000.

References: 1. Tostran® Summary of Product Characteristics. 2. Testogel® Summary of Product Characteristics. 3. Testim® Gel Summary of Product Characteristics. 4. Morgentaler A, et al. Steady-state pharmacokinetics. SMSNA Annual meeting 2011.

Date of preparation: December 2015. Job code: M015/1224(1)

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